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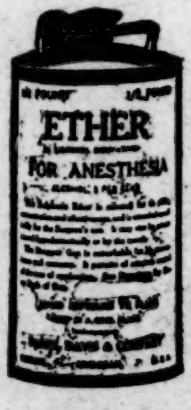

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The Journal of Laboratory and Clinical Medicine

VOL. I. ST. LOUIS, JANUARY, 1916 NO. 4.

ORIGINAL ARTICLES

GROWTH *

BY LAFAYETTE B. MENDEL AND THOMAS B. OSBORNE, NEW HAVEN, CONN.

THE solution of the chemical problems of growth has been approached along various avenues. One of these, and perhaps the earliest to be followed by any considerable number of investigators, leads to the *chemical analysis* of both growing and fully grown individuals. Its primary object is to disclose the characteristics of growth by a comparison of the chemical composition of organisms at various stages of their development. Despite the considerable abundance of data thus accumulated, relatively little of major importance has been contributed thereby to our knowledge of the subject. Growing cells and tissues may be morphologically and functionally unlike the fully developed structures into which they are finally transformed, but the analytical methods of the chemist of today are not sufficiently refined to reveal any eminently unique features of make-up characteristic of growth.

It is true that embryonic and other growing tissues are comparatively rich in water, and that the water-content diminishes to a certain degree with increasing age; but aside from such rather inexpressive generalizations respecting quantitative variations in composition at different stages of growth, no striking facts have yet been furnished by the devices of tissue analysis. Equally unprogressive has been the study of the comparative biochemistry of growth in the direction of qualitative analysis. From a purely biological standpoint it is of interest, and a result perhaps to have been anticipated, that there is a fixity, so to speak, in the composition of animal structures at various sizes of the same individuals. The number of the cells or the volume of each of them may be increased enormously; yet, broadly considered, the available analytical data show no striking differences in the chemical organization of the resultant protoplasmic mass in comparable tissues at various periods. In other words, aside from transitory depositions of reserve materials such as glycogen or fat, muscle remains alike in

*From the Sheffield Laboratory of Physiological Chemistry in Yale University and the Laboratory of the Connecticut Agricultural Experiment Station at New Haven, Conn.

its gross composition, and the nervous substance exhibits essentially the same chemical characteristic components, independent of age, diet, or environmental condition.

Several years ago a study of the composition of the bodies of mice kept upon diets of widely different types led one of us to express the outcome in these words: "The constant composition of the organism which is exhibited by our analysis, does not speak in favor of the possibility of depriving the body by alimentary procedures of any constituent excepting fat that is essential for its functions. On the contrary, it appears that the organism adheres to its proportionate composition. A deficiency in the diet, a lack of some food component, is not responded to by growth in which the tissue produced is chemically abnormal and shows a depletion in the missing factor. Its composition remains unaltered. Normal growth can proceed only when all the important constituents are assimilated in the proportions in which they make up the body. Losses are sustained only by the *uniform* disintegration of the tissues, whereby their relative composition remains unaltered."[1]

A more effective advance upon the chemical questions relating to growth has been made by the study of *nutrition* in this period of life. This more modern plan has meant a determination of what constructive units are essential for the building up of an adult organism, what materials must be furnished to the growing individuals, what possibilities of synthesis are inherent in them and will enable them to supply by construction the necessary tissue components. The successful pursuit of this method of inquiry depends upon the justifiable assumption, already mentioned, that protoplasm, if it is constructed at all, is not made into a fundamentally defective variety of diet, though deficiencies in the latter may lead to an unmaking of cells already developed.

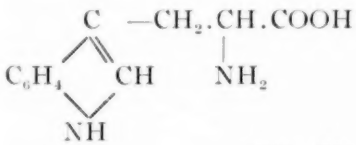
The questions relating to the initiation of growth and to the fundamental energy factors are not touched upon in this review. Certain modifying features of nutrition in growth are more or less obvious. The necessity for certain elements, like calcium, calls for no further comment here than to inquire to what extent the need of them is specific in growth. In the ordinary wear-and-tear of life, or what is technically designated as the maintenance metabolism, losses of structural elements call for restitution. In the case of the most of them we shall probably not err widely in saying that the metabolism of growth represents a highly exaggerated instance of the same needs, but on a scale appropriate to produce increment instead of mere maintenance of body substance.

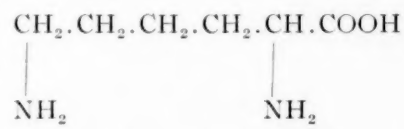
Modern chemical physiology has demonstrated in a convincing way that the diverse proteins which are now known to occur in nature can no longer be considered solely in a generic way in the roles which they play in the organism. These nitrogenous compounds lose their biological identity, even before they leave the alimentary tract, by becoming disintegrated into the chemical units—the amino-acids—out of which the proteins are built up. In so far as these amino-acids merely serve as fuel, it seems to matter little what their precise nature is. All of them can be, and usually are, destroyed readily in the metabolism. Inasmuch as tissue proteins are broken down in a small, yet seemingly inevitable degree in the wear-and-tear, the problem of satisfactory restora-

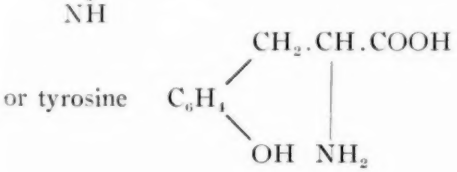
[1]Mendel, L. B.: Der Einfluss der Nahrung auf die chemische Zusammensetzung des Tierkörpers. Biochemische Zeitschrift, 1908, xi, 281.

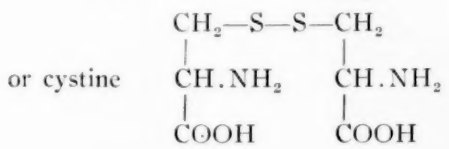
tion arises. During growth additional new protein molecules are to be provided. At the present time it may be said with confidence that many, though not all, of the amino-acids must be offered ready-made in the diet, because there is no evidence that they can be synthesized *de novo* even in growing mammals. For the lower forms of animal life this statement may not be valid, as it is not in the case of plants. In the higher forms, however, the exhibition of dietary proteins which are deficient in respect to their yield of any of the essential amino-acids may be expected to lead to suppression of growth and even failure of maintenance, depending on the degree and nature of the structural shortcomings.

The evidence in support of this general statement has resulted from the possibility of preparing a ration which is complete or adequate for growth in every respect other than the protein component. This latter factor can then be added experimentally in any way desired. The casein of milk is one of a few proteins which fail to yield the amino-acid glycocoll $\begin{vmatrix} CH_2.COOH \\ | \\ NH_2 \end{vmatrix}$ upon analysis. Tissue proteins, and particularly those of the omnipresent connective tissues, include a relatively large content of the glycocoll group in their make-up. Yet animals can be grown to maturity and into a second generation upon a diet containing the glycocoll-free casein as practically the sole source of food protein. Here, then, is a striking illustration of the capacity of a growing organism to supply, by synthesis, one of the essential amino-acid constructive units of its protoplasm. On the other hand, there are proteins, particularly of vegetable origin, which fail to furnish one or more of the amino-acids, such as tryptophane









which tissue proteins also yield. As the result of very recent experimental investigation there is little room for doubt that all of these mentioned amino-acids must be furnished ready-made to an organism for the constructive uses of growth. The organic chemist will appreciate why the laboratory of the living cells may be unable to synthesize nuclei so complex as those of tryptophane or tyrosine and yet be competent to produce a comparatively simple product like glycocoll.

The best proof of the indispensability of some of the amino-acids has been furnished by actual feeding experiments. Without the proper complement of these units, even the best diet spells disaster; and the addition of the missing ones, either as such or in the guise of proteins containing them, brings renewal of growth proportionate, as a rule, to the extent to which the deficiencies are made good quantitatively as well as qualitatively. The lack of an essential pro-

tein factor need not be an absolute one to produce malnutrition. It has become apparent, as Abderhalden pointed out long ago, that where the organism cannot synthesize an essential fragment, the nutritive pace is set, so to speak, by the minimum of any indispensable dietary ingredient. In practice this means that however abundant in protein and seemingly "balanced" a diet may be from the standpoint of the theories of nutrition of a generation ago, it is certain to be inadequate for growth if the proteins are qualitatively unsuitable as in fact they may be if derived from a single source.

For the problems of practical dietetics and particularly of animal production it is further of interest to note that chemically identical proteins are apparently not present in animals or plants of different species unless they are biologically closely related. In so far as the differences are an expression of inequalities in the amino-acid make-up of the protein from these varied sources they are likely to have significance in the construction of a dietary suitable for growth. There are various protein by-products, for example from the cereal, milk and meat industries, which are available as low priced nutrients and the successful use of which must henceforth be determined, in so far as they enter largely into the rations of growing animals, by the standard of their competence to furnish the essential amino-acids suitably. It has been shown that unquestionable differences exist in the economy of correcting various inadequate protein foods with appropriate supplementary proteins. The problem seems in part at least to be one of suitably combining products that are deficient in one or more nutrient units so that the mixture shall not have any serious relative shortage of any one of them.

The upshot of these newer developments in the physiology of nutrition has been to give a new trend to the biochemistry of the proteins and to lend a greater importance to this pre-eminent group of food stuffs. Those whose field of interest lies far away from these strictly chemical aspects of nutrition will appreciate the comment of one of our colleagues (von Fürth) when he says: "I invariably experience a feeling of envy when I read the letters of Liebig, Wöhler, or Berzelius, and note how important an event for these fortunate individuals was the appearance of every scientific publication. With what devotion and joy they read and re-read every detail of even the smallest scientific contribution. Today, owing to the great mass of scientific literature, we are in danger of losing the naive pleasure which anything novel should afford; and we are likely to sacrifice the spirit of inquiry or inquisitiveness that attaches to the soul of the man of science. And so, today when the devotee of biochemistry, working in the sweat of his brow, is barely able to orient himself in the essentials of its literature, familiarity with its content has long since become an impossibility for him who stands apart from any immediate concern with such topics." (v. Fürth: Probleme, i, p. 2.)

And now, at a time when the energy problems of growth have reached a degree of solution that gives a clear and fairly comprehensive insight into this aspect of nutrition, so that this chapter of physiology can at length be reviewed with a fairly satisfactory understanding of what it involved, entirely new questions have thrust themselves into the foreground. Physiologists have long realized that the ideal way to study the problems of nutrition would be by feeding

artificial mixtures of the isolated and purified nutrients. The successive failures of the attempts in this direction, which need not be detailed here, coming in conjunction with evidence from other sources, have awakened us to the realization that perhaps something more than the familiar proteins, fats, carbohydrates and inorganic nutrients are essential to the persistence of the life processes or the accomplishment of prolonged growth. The modern researches on the physiological significance of the secretions of the ductless or so-called endocrine glands and the growing evidence for the regulatory function of hormones or chemical stimulants distributed by the circulation have made it easier to believe that substances which are neither significant as sources of energy nor sufficiently abundant to construct new portions of protoplasm may nevertheless exercise a dominant effect upon nutrition. To one who has been brought up in the study of exact stoichiometric relations in science there is something almost unscientific and mystical in the discovery that mixtures of food stuffs which are selected from the chemist's supplies and fail to maintain animals can be made adequate by the addition of milk, for example, in quantities far too small to have significance as a source of energy. We are dealing here with what have been called food accessories or "vitamines."

Growth appears to be in some degree dependent upon the presence of chemical determinants of this order. For the present they must not be confused with other known essential nutrients, with suitable amino-acids, or inorganic salts, or appropriate carbohydrates. It must be recognized, at the outset, that unless the conditions are suitable for maintenance, growth which is normally superimposed upon it, cannot proceed. The value of food accessories of as yet unknown chemical nature has been made evident of late by feeding experiments with isolated food substances, where additions of small amounts of naturally occurring products have prevented nutritive decline or brought restoration. This is notably true of the "protein-free milk" devised by Osborne and Mendel for feeding rats. No artificial imitation of this natural mixture, which contains milk sugar, inorganic salts and very small quantities of unknown ingredients, has been devised to replace it satisfactorily for considerable periods of growth. The success of the "natural" product seems to be dependent upon the presence of undiscovered "determinants" in minute traces. Evidence for the existence of such accessories is further furnished by the so-called deficiency diseases. In some cases heating seems sufficient to destroy some thermolabile determinant of maintenance. The development of scurvy from the use of heated foods is an illustration of this point.

It is not unlikely, in the light of the meager data now at hand, that there is more than one determinant or food accessory that promotes suitable maintenance. There is no justification whatever for including these unknown factors today in a common chemical group aside from the fact that they seem to be essential and to act in small amounts in ways not hitherto taken cognizance of. Some of them are unquestionably quite thermostabile, others are perhaps thermolabile. With the possible exception of Funk's beriberi "vitamine" they have hitherto eluded chemical identification. Perhaps they merely stimulate the appetite and thus induce an adequate food intake; though this explanation seems to be clearly contradicted by some of the existent reports. Perhaps they merely

supply cell adjuvants like iodine or manganese or some organic compound, the need of which we have overlooked because it is quantitatively so small. In any event they represent an undetermined factor that must be reckoned with.

However, an adolescent animal may actually fail to grow upon a diet which serves well to maintain an adult individual of the same species. Grown rats have been kept in good health for many months on a ration consisting of protein, sugar, starch, "protein-free milk" and lard. Upon this diet the young of the same species grow for a limited period and then invariably decline. We have had the almost paradoxical experience that those animals which grow on the diet mentioned presently die, whereas those which do not experience growth are more likely to continue to live. This may be interpreted to indicate that in growth an essential substance presumably stored in some measure in the adolescent organism is used up, whereupon nutritive failure ensues; whereas in the absence of active growth a depletion of the material so necessary does not take place in the same degree. It has been shown that this cessation of growth can be stopped and growth resumed by the substitution of other naturally occurring fats for part of the lard of the ration. In butter-fat, egg-fat, cod liver-fat, and beef-fat,—and more specifically in the fractions of these containing the oil components liquid at ordinary temperatures—there exists a determinant of growth in the sense in which this expression has been discussed above. It is apparently not a nitrogenous or phosphorized compound like the phosphatides which have been charged with growth-promoting effects, but experimentally its action is pronounced in rats. When other factors, such as suitable proteins or salts, are missing the chemical accessories yielded by the natural fats are obviously incapable by themselves of insuring growth.

How or why do these chemical determinants promote growth? The best that we can do today is to recite the facts. Perhaps they promote appetite and lead to gain of weight by inducing suitable food intake. It is not easy to reconcile such a hasty explanation with the marked differences between the fats studied. Perhaps they merely represent chemical ingredients necessary at all times for the body cells, but needed in great abundance during increment in size and therefore not available in sufficient amounts in a diet adequate for mere maintenance with limited wear-and-tear or tissue loss. These problems are still with us.

THE GENERAL PATHOLOGY OF PELLAGRA, WITH SPECIAL REFERENCE TO FINDINGS IN THE THYROID AND ADRENALS*

By Plinn F. Morse, M.D., Detroit, Mich.

PELLAGRA is interesting from the standpoint of pathology because it bears a rather unique place among the well-known clinical conditions. No disease has been more thoroughly studied from most standpoints and less thoroughly from that of its general pathology. The incidence, geographical distribution, mortality, relations to diet and to possible infective sources, have been the subject of extensive investigation by many organized commissions and independent observers, but perusal of the reports from these sources gives one the impression of marked one-sidedness in the method of attack, for the reason that there seem to be no recent examinations by modern methods of the pathological anatomy of the disease as a whole. All the recent complete studies have been focused especially on the nervous system, and Harris states that he has no doubt but that pellagra will be found to be essentially a nervous disease when the problem is finally solved. Such excellent studies of the histopathology of the nervous system appear in the literature that it is not necessary to do more than review them. Concerning other organs and tissues however very little has been said recently. The bibliography up to 1910 and the pathological findings up to that time are reviewed by Lavinder and Babcock in their translation of Marie's book. Nothing has been added since except more detailed studies of the nervous system.

The pathological findings up to 1910 as abstracted from Lavinder and Babcock's review of the literature are briefly as follows:

Central Nervous System.—Pigmentary, granular, and fatty degenerations of the nerve cells, occasional loss of myelin around the axis cylinders, varying degrees of degeneration and sclerosis of the posterior and the lateral pyramidal tracts. The degeneration in the posterior columns differs from tabes in certain important respects. The increased pigmentation of the posterior root ganglia described by Lombroso is one of the most important constant changes. Belmondo, cited by Lavinder and Babcock, naively states that this pigmentary change occurs even in the "youngest cells of the ganglia," not recognizing the fact that all nerve cells are of prenatal origin. A large number of inconstant concomitant changes common in many other conditions, such as hemorrhage, intercurrent myelitis, osteomata of the arachnoid, thickening of the meninges and adhesions to the skull cap, myelin droplets in various parts of the cord, etc., are described by various authors in detail.

Arteriosclerosis of the vessels of the central nervous system and its results have been frequently noted.

Lungs.—Accidental complicating lesions such as emphysema, pneumonia, edema, congestion, tuberculosis.

Heart.—The constant and striking change has been extreme brown atrophy

*From the Buhl Memorial Laboratory of Harper Hospital, Detroit.

of the heart muscle. Hypertrophy, atrophy, atheroma, hydropericardium and aneurism have been occasionally met with.

Liver.—Brown atrophy was the most constant change, congestion and fatty infiltration were sometimes found.

Spleen.—Atrophy.

Kidneys.—Atrophy, fatty changes in the tubules, and increase of interstitial connective tissue.

Intestines.—Muscular atrophy of the wall, hyperemia and ulceration of the rectum. Other changes, such as anemia and hyperemia, chronic enteritis, and thickening of the Peyer's patches have been accidental and less constant.

Suprarenal capsules, pancreas, and testicles are reported as normal. No definite references to microscopical appearances are made.

Female Sexual Organs.—These showed many noncharacteristic lesions of common occurrence in other conditions.

Muscular System.—Atrophy was the most constant finding.

Skeleton.—Fragility of the ribs and other bones dependent upon eccentric atrophy was frequently observed along with evidence of increased blood destruction in both the marrow and the spleen.

The most complete study of the central nervous system in pellagra made in this country is that of Harris who confirmed the work of Babes, Scion, and Marinesco and added certain important features. Harris described small collections of lymphocytes in the brain and swelling of the neuroglia in association with the vessels. Hitherto undescribed changes in the Purkinje cells probably explaining the ataxic form of the malady were brought out by him. A more recent minute study of the nervous system in pellagra has been made by S. A. K. Wilson, who lays stress on the degeneration of π granules of Reich, and marked degeneration of the cells in Clark's columns. Wilson believes that the degenerations found in the cord are pseudo-system degenerations.

Skin.—The findings in the skin are not reported as very striking or characteristic. There has been a rather constant increase of the horny layer with marked desquamation, the stratum Malpighii has been found atrophic, and the corium sclerotic with thickening of the vessels, and perivascular infiltration. Gurd has described these changes in detail and has considered, as others have before him, the changes due to the action of actinic rays upon abnormally sensitized skin.

Specific references to the ductless glands are rare. Harris and Wilson both state that examinations of the ductless glands in their cases were made and the organs found normal.

An interesting clinical finding of great importance is the occurrence of a lymphocytosis as reported by Hillman and Schulle, and others.

The clinical history of the patient from whom the material here reported was obtained is briefly as follows:

Mrs. W—, Widow, age 38, housewife, English, admitted to Harper Hospital on September 24, 1915, on the service of Dr. Haass.

Patient complained of weakness, diarrhea, "sore arms" and "cloudiness in head," the duration the patient stated to be about four months. It was very difficult to obtain an adequate history on account of the patient's marked mental

torpor bordering at times upon amentia. Family History. No clear statements obtainable relative to diseases or cause of death of parents or other relatives. Personal History: Husband died three years ago of tuberculosis. One child twelve years of age, living and well. She has worked for some time in a chandelier store as scrub woman. Came to this country two years ago. Patient cannot remember any other sickness in her life. Has not menstruated for seven months.

Present Trouble.—Has not been feeling well for last seven months since she stopped menstruating. Her appetite has been poor with an occasional headache and dizziness. For the last four months patient has had a diarrhea constantly. She has been bothered by "cloudiness and haziness in the head," poor memory, irritability, headache, weakness, and dizziness. A skin lesion appeared four months ago, first between the fingers on the backs of the hand; it gradually spread involving the hands and extensor surfaces of the forearms, the knees, feet and neck then became involved to a less extent. The patient dreads food and even liquids because they nauseate her and give her diarrhea. She is unable to taste anything and her mouth is dry and sore. She sleeps poorly and of late has lost control of her rectal sphincters. (Ulceration?)

Physical Examination.—The patient is a medium built woman with dull expression and staring eyes. Poorly nourished scalp with hair rapidly thinning. Pupils equal and react to light and accommodation. The lips are dry with corners eroded and are partly covered with a silvery gray coat. There are erosions of the mucous membrane of the mouth and the tongue is reddened and swollen. There are no palpable glands. Heart and lungs, negative. Abdomen, tender and flaccid; liver and spleen, not palpable. On extensor surfaces of the hands and forearms the skin is thickened, cracked and pigmented, with deep wrinkles, resembling the skin of a very old person except that it is thick, hard, dry, and pigmented. The skin is so much thicker in the portion involved that taken with the distribution the lesion gives the impression of a glove. The coloration varies from a narrow zone of bright pink erythema around the edge to dark brown in the thinner portions of the lesion and a brownish-yellow in the thick leathery expanse of the lesion proper. The same condition is present over the knees, on the backs of the feet near the toes, and around the neck in the manner of a pendant. The reflexes are sluggish and sensation is delayed especially over the involved area. The patient has not been able to stand on her feet for several weeks probably because of weakness.

White cell count.—7,300 Polys., 53%; Small lymphocytes, 38%; Large lymphocytes, 6%; Transitionals, 3%; Hemoglobin, 75%.

Wassermann.—Negative. Urine negative. Temperature very irregular, varying from 97 F. to 101 F. Examination of stools on warm stage revealed no amebae or other parasites.

A diagnosis of pellagra was made by Dr. Haass and the patient referred to the dermatological service of Dr. H. R. Varney who concurred in the diagnosis.

It later appeared that the patient has been at the Woman's Hospital and turned over to the Poor Commission by Dr. Vernier as a pellagrin. The Poor Commission sent her to St. Mary's Hospital where the diagnosis was made by a house physician who had resided in the South. The case was immediately deported from

St. Mary's Hospital by the Sister in charge under the impression that pellagra was contagious. She was then sent to Harper Hospital and was later examined by Lieut. Weber of the Public Health Service who concurred in the diagnosis and was arranging for her deportation as a diseased alien when she died. It is therefore thought that the characteristic combination of skin lesion, gastrointestinal disease and profound mental disturbance coupled with the confirmation of several independent diagnoses made by various physicians all of whom have had experience with pellagrins, make the diagnosis certain.

The patient died on October 4th at 10 a. m. Autopsy was performed at 3 p. m. of the same day.

Autopsy Notes.

The body is that of an emaciated female apparently about 40 years of age. There is moderate overgrowth of hair over the body with somewhat of a masculine type of distribution. Eyes and nose negative. Mouth shows marked pyorrhea and a bluish line on the gums somewhat resembling that of lead poisoning. The buccal mucosa is ulcerated, the tongue red at the margins, dry and cracked, with a heavy yellowish coat toward the center. Both hands and arms present marked skin changes. On the extensor surfaces it is very thick and wrinkled with marked pigmentary deposit. The outer borders of the lesion are dark brown in color and the rest a brownish-yellow. The skin appears edematous and thickened and is extremely wrinkled. There is increased desquamation. The lesion ends on the extensor surface toward the elbow in a rather "V" shape. Both knees show the same lesion. The backs of the feet near the toes show less advanced lesions there being not so much thickening and more desquamation. Around the neck somewhat in the shape of a turned-in shirt the lesion appears with patches of more intense involvement here and there along its course. Section shows the fat of the abdominal wall to be deeply pigmented and yellowish. The muscles are dry and pale. There is no gas or fluid in the peritoneal cavity. The liver is five finger-breadths below the costal margin in the mammary line. The omentum is congested, the appendix retrocecal and somewhat dilated. Superficial topography of the abdomen otherwise negative. Thorax: The sternum is narrow; the bony prominences at junction of the costal cartilages and ribs somewhat elevated. The sternum is very rich in deep red marrow. The pleurae are free from adhesions and there is no fluid. The heart is dilated; the apex is two inches outside the mammary line at the sixth interspace. Small amount of amber fluid in the pericardium. Heart negative over outer surface. Left ventricle empty, mitral admits two fingers. The muscle of the left ventricle is thinner than normal, deep brown in color and the endocardium shows well-marked fatty striations. The mitral flaps are thickened and somewhat shortened but present no other abnormal appearances. The right ventricle contains a postmortem clot; the wall is thin and similar in color to the left. The tricuspid admits four fingers, but the flaps are normal. The pulmonary artery contains a postmortem clot. The semilunars of the pulmonary are negative. The first portion of the aorta shows a moderate linear sclerosis. The semilunars of the aorta are normal. The left coronary is very markedly sclerosed, showing nodular and linear thickenings with narrowing of the lumen

throughout its extent. The systemic aorta presents an especially marked patch of sclerosis at the celiac axis. The heart weighs 175 grams. The right lung weighs 325 grams, crepitates throughout, is moderately anthracotic and dry on section. At the root are calcified anthracotic lymph nodes (healed tubercles). The left lung is similar to the right but is more anemic; weighs 220 grams.

Neck Organs.—Pharynx and esophagus normal. Larynx negative. The trachea presents a sero-mucous exudate. The tongue is thickened, dry, reddened and cuts with more resistance than usual. There are at first apparently no thyroid lobes, but careful dissection reveals two fibrous plates, about a quarter of an inch thick, which occupy about the surface area of the normal thyroid and have its position. Both of these plates taken together, upon being dissected out weigh ten grams. No parathyroid bodies can be found in this dense mass of connective tissues.

Liver.—Weight 1,550 grams. The surface shows an irregular yellowish mottling. On section it offers increased resistance to the knife and has a distinct fatty shine. *Adrenals:* The adrenals show marked hypertrophy. Their combined weight is 27 grams. *Kidneys:* The left kidney weighs 135 grams, is quite soft and swollen, dripping blood freely. The right kidney weighs 175 grams and is similar to the left. *Gastro-intestinal Tract:* The gastric mucosa is congested and shows some small erosions and petechial hemorrhages. The pyloric region is normal. The duodenum shows no lesions beyond congestion. The small and large intestine show no lesions except that there is marked postmortem dilatation of the small and large bowel with thinning of the wall. There is a large area of ulceration with granulation tissue from the internal sphincter to the anus. *Pelvic Organs:* There are old adhesions between the sigmoid, uterus, and adnexa.

Brain and Cord: The skull-cap is normal. No thickening of the dura is observed and the sinuses contain only a little postmortem clot. The brain presents no gross changes; there is no apparent thickening of the pia mater and the convolutions are normal. The base of the brain shows no abnormalities. (The brain was put in formalin and further section done about two weeks later without any gross changes being disclosed.) The cord presents no gross changes.

Microscopical Findings.

Adrenal.—Sections of the adrenal glands were fixed in formalin and Zenker's fluid, and longitudinal and cross-sections stained in hemotoxylin and eosin. The relations of cortex and medulla are about normal. The medulla presents a beginning postmortem digestion. The cortex shows normal relations of the glomerular, fasicular, and reticular zones. There is perhaps some decrease in the prominence of the fatty droplets of the cortical cells. The medullary zone is remarkable for the marked dilatation of the blood sinuses and of the small capillaries (Plate III, Fig. 7). The chromaffinic cells are somewhat reduced in number and there is a very moderate fibrosis of the medulla. Around all the large vessels and also scattered diffusely through the adrenal medulla, we find focalized collections of lymphocytes (Plate III, Figs. 8, 9, 10). These show a definitely infiltrative chronic inflammatory reaction with a few plasma cells (Plate

PLATE I.

Fig. 1.
Thyroid, showing sclerosis and round-celled infiltration. Area of adenomatous gland at margin.

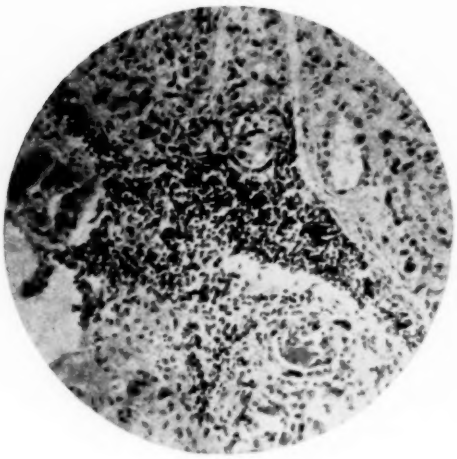


Fig. 2.
Thyroid, high power, showing round-celled infiltration.

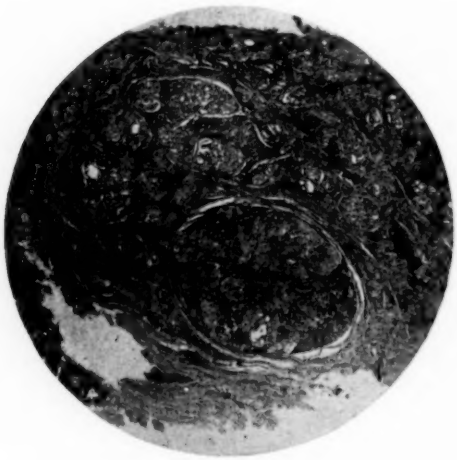


Fig. 3.
Thyroid, low power, showing widespread sclerosis of gland.

PLATE II.

Fig. 4.
Skin, high power, showing infiltration and sclerosis. Margin of active lesion.

Fig. 5.
Skin, low power, center of old lesion.

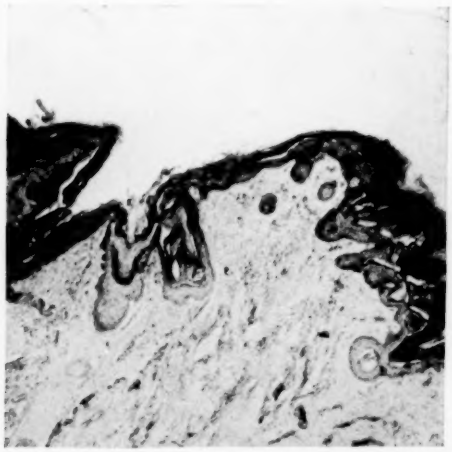


Fig. 6.
Skin, old lesion.

IV, Figs. 11 and 12). The adrenal presents the general picture of moderate atrophy of the medulla with practically no changes in the cortex. In this atrophic medulla we find great dilatation of the blood-spaces and round-celled infiltration focalized especially around the blood vessels.

Heart.—Sections made from both ventricles show moderate hypertrophy of individual muscle cells with a subsequent brown atrophy of extreme degree. There is irregularity in the size and staining properties of the nuclei. The heart muscle is engorged with blood and all the small capillaries are dilated. One area of myocardium has undergone anemic infarction (Plate VI, Fig. 18). The cells are dead but there is no connective tissue reaction as yet. This is to be interpreted as a recent event due to the very advanced sclerosis found in the left coronary artery. The endocardium is moderately but diffusely thickened throughout. This thickening consists merely in the laying down of connective tissue, probably representing a senile or nutritional change; there is no round-celled infiltration or other sign of active endocarditis. The most striking change found in the heart is the extreme degree of brown atrophy, a condition which has been noted before by Lombroso and others. Sections of the blood-vessels show throughout a more or less marked degree of sclerosis. It is interesting that the sclerotic changes in the left coronary artery (Plate VI, Fig. 19) far outstrip those of any other vessel. The sclerotic changes of the aorta consist of a moderate diffuse fatty change beneath the intima, with an occasional erosion of the surface. There is very slight connective tissue reaction. The elastic membranes of the aorta do not seem to be greatly reduced in number. The diffuse bluish cast of the whole media would suggest an early stage of calcification without any definite areas being present. No round-celled infiltration appears, either in the media or in the vascular areas of the adventitia. The sclerosis of the coronary has gone on to an advanced stage. There is extensive calcification of the media with large calcified plaques extending for some distance along the wall of the vessel. Both the left coronary and its branches are extensively calcified.

Thyroid.—The changes in the thyroid are more striking than those of any other organ of the body. There is practically no thyroid tissue present that might be considered in any sense normal. The gland consists of a mass of new and old connective tissue (Plate I, Figs. 1, 2, 3) infiltrated with round-cells, through which, interspersed here and there are islands of thyroid tissue either being destroyed by the pressure of the surrounding connective tissue, or proliferating and adenomatous acini in small encapsulated areas like those found in old degenerating goitres. These follicles contain no colloid but are gland acini with columnar or high cubical epithelium; only very rarely is seen an atrophic follicle with a small mass of shriveled colloid. There is one area of this adenomatous tissue slightly larger than the rest and well encapsulated. The amount of glandular tissue as a whole is extremely small. The picture presented by this thyroid is unique in that it is a true chronic interstitial productive thyroiditis. There is marked increase of connective tissue, old connective tissue showing hyaline change, and areas of young connective tissue around areas of extreme round-celled infiltration. This inflammatory reaction has gone to the point of almost total glandular destruction, so that only small islands of gland-

PLATE III

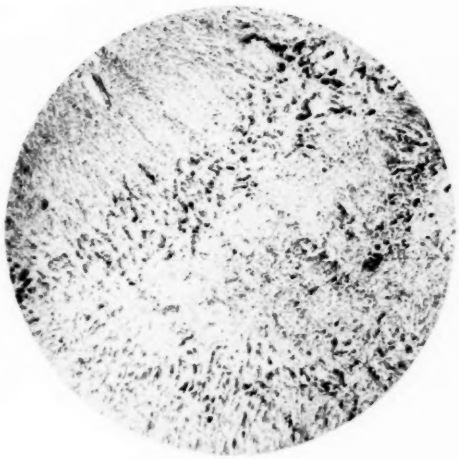


Fig. 7.
Adrenal, low power, showing dilated blood spaces and fibrosis of medulla.

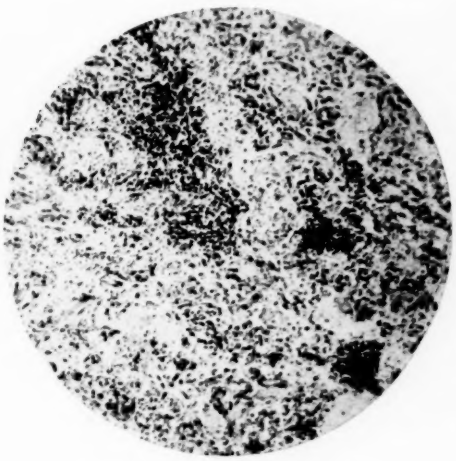


Fig. 8.
Adrenal, infiltration in medulla with fibrosis.

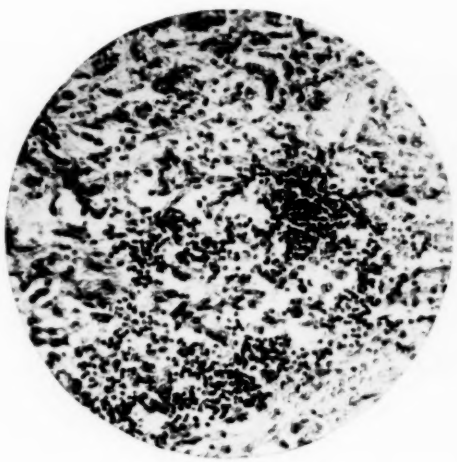


Fig. 9.
Adrenal, high power, showing infiltration in medulla.

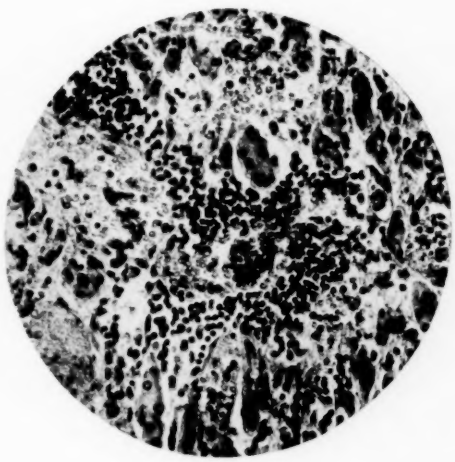


Fig. 10.
Adrenal, chromaffinic tissue associated with round-celled infiltration in the medulla.

ular tissue are left, and they, probably in an effort to compensate for the embarrassed glandular function, have taken on abnormal appearances. No thyroid ever examined by the writer has ever presented this picture. It is not the picture of any of the well recognized types of thyroid disease. The round-celled infiltration consists almost entirely of lymphocytes but plasma cells are occasionally found. The picture suggests not so much an infective process as the reaction to some chronic intoxication with gradual destruction of the gland by the inflammatory reaction, inasmuch as the usual picture of an infective type of inflammation is absent, and we get rather the idea of a diffuse sclerosis due to some diffused chemical irritant, than of infection with its focalized manifestations in the organ. The picture reminds one of an old sclerotic kidney except that the process is more active as is evidenced by the round-celled infiltration.

Hypophysis.—The hypophysis as a whole is larger than normal. Sagittal sections of the hypophysis were fixed in formalin and in Zenker's fluid, and stained in hemotoxylin. Microscopical examination reveals nothing of interest, except perhaps some increase of the colloid follicles of the pars intermedia. The pars anterior shows the normal basophilic cells in the normal proportion. The large blood sinuses are engorged with blood. There is no round-celled infiltration. The capsule is not thickened, and there is no adenomatous hyperplasia of the cellular portion. The pars nervosa is about normal in extent and presents no abnormalities of structure.

Gastrointestinal Tract.—The stomach presents no striking abnormality. There is a disappearance of the acidophilic cells and prominence of the mucous forming acini. The muscularis shows no marked atrophy. There is a moderate congestion of all the coats. The lymph follicles are normal in size and number. There is no erosion of the surface, no ulceration and no round-celled infiltration, in the sections examined. Except for the marked disappearance of the acidophilic cells, the stomach must be considered normal. Passing into the duodenum we find the thickness of the wall fairly normal. There is marked congestion, especially of the vessels of the villi. The epithelium of the villi is all gone (postmortem change) and the villi appear more fibroid than normal. There is no evident atrophy of the muscularis and no round-celled infiltration anywhere in the duodenal portion of the intestine. Brunner's glands are normal in appearance. Farther down the small intestine the same conditions are noticed; the villi are hypertrophic, fibroid and congested and totally eroded of epithelium, except for the bases of the crypts. There is no marked atrophy of the muscularis as is described by most writers and the brown pigmentation is much less prominent than some reporters have found. The lymphoid apparatus of the intestine is rather atrophic. Contrary to the findings of some other observers, the Peyer's patches are atrophic and possess few germ centers. No ulcerations were found anywhere in the intestinal tract, except at the anus. The large bowel presents the same changes as the other portions of the intestinal tract (Plate VI, Fig. 20), except that there is more extreme stasis here than in any other portion of the gut. The fibroid change of the mucosa is also somewhat more marked. There is the same erosion of epithelium. No definite atrophy of the muscularis can be made out. The lymph tissue is also somewhat atrophic. There is increased mucous formation and cystic change in portions

PLATE IV.

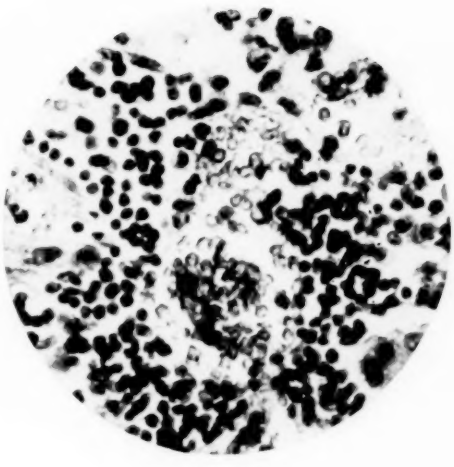


Fig. 11.
Adrenal, high power, perivascular infiltration around a capillary.

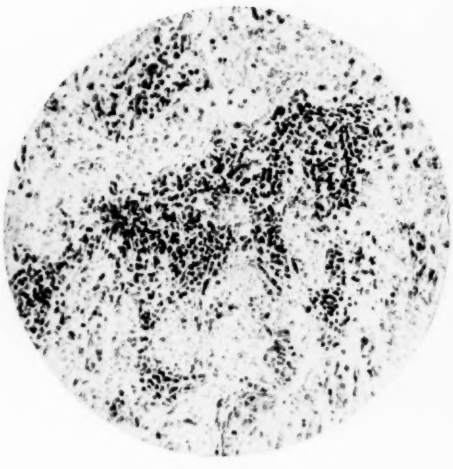


Fig. 12.
Adrenal, diffuse infiltration of medulla.

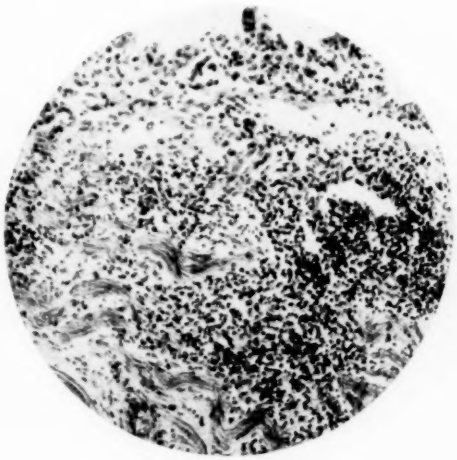


Fig. 13.
Rectum, ulceration and infiltration.

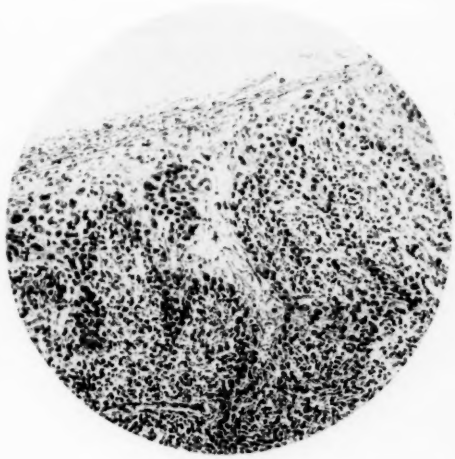


Fig. 14.
Tongue, active, subacute and chronic glossitis.

of the mucosa of the large bowel. Throughout the gastro-intestinal tract the nerves present a rather striking appearance. The cells of the endoneurium appear swollen and more bluish than normal. They are enlarged and oat-seed shaped as though they were edematous. The nerve fibers are unusually prominent. Whether this is due to the swelling of the fibers or to a possible atrophy of the muscularis might be debated. The writer does not believe that the muscularis is especially atrophic.

Near the anus is a rather large area of ulceration which microscopically presents an active infiltrative inflammatory picture (Plate IV, Fig. 13). The mucosa is eroded, the epithelium being replaced by granulation tissue actively infiltrated by round cells, which extend down to the deeper layers of the muscularis. There is here, then, a deeply destructive ulcerative process of the anus. There is not the marked atrophy of the muscularis in this case that most writers describe although the gross impression of muscular thinning was much greater than the microscopical appearances warranted.

Tongue.—The tongue (Plate IV, Fig. 14) presents a very striking appearance. There is marked atrophy of the epithelium with fraying out of the upper layers of the epithelium suggesting an atypical horny layer. The subepithelial tissues present a picture of extreme congestion and intense round-celled infiltration; a marked subacute but active glossitis.

Pancreas.—The pancreas presents no abnormal appearances either of the acini, ducts, islands or Langerhans, connective tissue, or blood-vessels.

Liver.—The liver shows chronic passive congestion with dilatation of the capillaries and corresponding atrophy of all the liver cells.

This picture is rather interesting, in that the blood is not collected especially around the central vein with atrophy and necrosis of the central cells as is usually the case, but the engorgement is universal throughout the liver, and the atrophy is diffuse and uniform throughout the lobule. This suggests a primary liver atrophy rather than one due to chronic passive congestion. Occasionally we come upon small focalized areas of round-celled infiltration, including plasma cells and occasional eosinophiles not in association with the islands of Glisson, but rather with the central or sublobular veins. Contrary to the impression obtained from gross inspection, no fat is found. The individual liver cells are swollen and edematous.

The *striped muscle* presents postmortem coagulation changes resembling Zenker's necrosis.

Genitourinary tract.—The cervix shows old ectropion and partially healed erosion, with chronic endocervicitis. Large cystic glands containing a large amount of mucous are present. Just inside the external os there is an area of polypoid granulation tissue extending down to the mouths of the glands and forming polypi on the surface.

The bladder mucosa is normal, except that one section shows a small area of round-celled infiltration around one of the vessels, and a very small area of round-celled infiltration in the mucosa in one place.

The kidney shows marked atrophy. There are many more glomeruli in a field than normal. There is no increase of connective tissue, either diffusely or around the vessels, and no vascular sclerosis. The tubules show no changes and

PLATE V.

Fig. 15.
Posterior spinal ganglion, low power, showing degeneration.

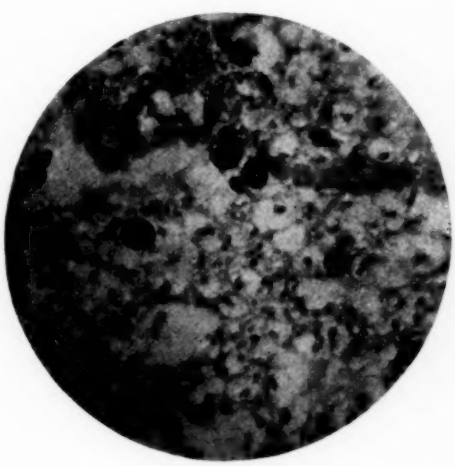


Fig. 16.
Calcified myelin droplets (?) in spinal cord.

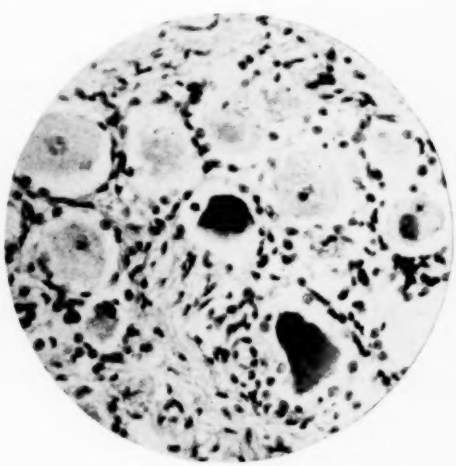


Fig. 17.
Cells of spinal ganglion, showing degeneration of individual cells.

there is no round-celled infiltration. The only lesion presented by the kidney is one of extreme atrophy coupled with edema and congestion. The nephritic changes so commonly observed are lacking.

The ovary is atrophic. There is no general increase in connective tissue although there are a large number of corpora albicantia. The ovary is markedly congested. No active Graafian follicles are found. Both ovaries are the same size and neither is cystic. The tubes are normal, except for dilated varicose veins on their peritoneal surface. The uterine endometrium shows an extreme grade of atrophy although the vessels show less sclerosis than is usual with this extreme grade of atrophy of the endometrium.

Lung.—The lung shows moderate atrophy and anthracosis. There is an area of perivascular round-celled infiltration in the neighborhood of a large bronchus, near a small island of cartilage.

Central Nervous System.—The posterior root ganglia (Plate V, Figs. 15, 16, 17) present marked degeneration of individual cells, with marked shrinking and nuclear degeneration. There is striking brownish pigmentation of the ganglion cells as described by Lombroso and others. The spinal cord shows no sclerosis of any one particular tract but there is a general thinning of the myelin sheaths and numerous dark blue staining bodies (hematoxylin) from 20 to 50 microns in diameter distributed along the subpial region of the posterior columns and along the intramedullary portion of the posterior roots. The writer believes that many of the appearances described as degenerations of nerve cells are postmortem changes and does not feel capable of reporting upon the nerve cell changes found in this case until he has had opportunity for further study and comparison. These bluish bodies have been observed in many pathological conditions, and may also be postmortem changes. A more complete report on the histopathology of the nervous system in this case will be made in the near future.

Skin.—The skin presents several important changes. There is marked hyperkeratinization of the epidermis everywhere (Plate II). The stratum Malpighii is markedly atrophic and in places the rete has dipped down deeply into the corium (Plate II, Fig. 6). The corium shows dilated fibroid vessels and increased amount of fibrous tissue with decrease in elastic tissue. The hair follicles are atrophic and deformed and are surrounded by rather thick sheaths of hyalin connective tissue (Plate II, Fig. 4). The sebaceous glands are almost absent and only fibroid remnants of them are to be found around the base of the hair follicles. The sweat glands are fairly normal, perhaps show a slight fibrosis. Here and there we find throughout the stratum corium areas of round-celled infiltration (Plate II, Fig. 4), usually perivascular but not always. This Gurd interprets as a healing reaction to the injury caused by light on the sensitized skin.

Spleen.—There is the usual picture of atrophy. The sinuses are engorged with blood. No evidence of increased blood destruction as reported by some observers is seen, either as evidenced by phagocytosis of red cells or increased pigmentation.

Bone-marrow.—The red marrow is increased in quantity and very active throughout all the bones. Microscopically the sections of the marrow are normal except for a general hyperplasia as is seen in any moderately severe anemia.

PLATE VI.

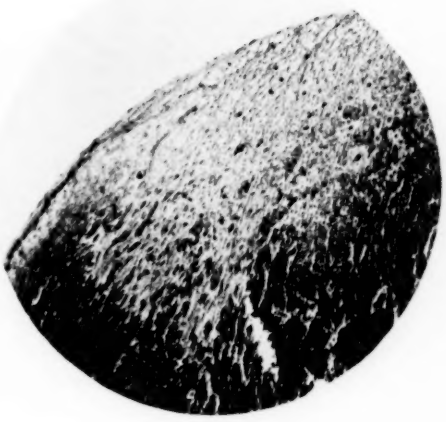


Fig. 18.
Anemic infarct of heart.

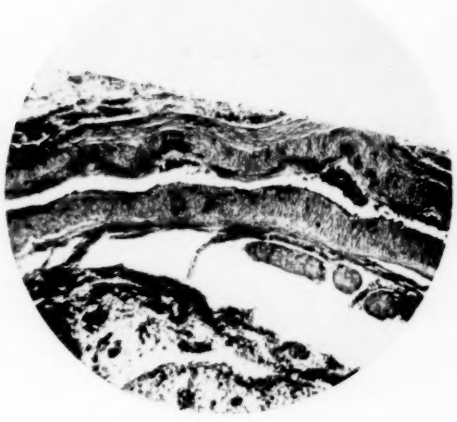


Fig. 19.
Sclerosis of coronary.

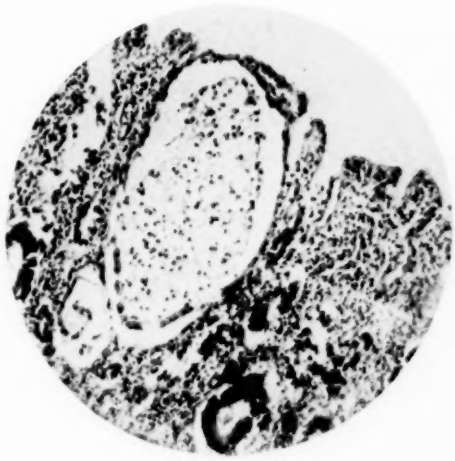


Fig. 20.
Large intestine, showing postmortem change and cystic degeneration of a gland.

SUMMARY OF POSTMORTEM FINDINGS.

Simple or brown atrophy of the heart, liver, spleen, lungs, intestinal muscles (?) and kidneys.

Degenerations and brownish pigmentation of the posterior root ganglia (and other groups of nerve cells).

Active ulcerative proctitis and chronic glossitis of marked degree.

Hyperkeratosis and sclerosis of the skin with areas of round-celled infiltration.

Hitherto undescribed changes of inflammatory nature in the thyroid and adrenal. The lesion in the thyroid being a marked example of chronic productive interstitial thyroiditis with compensatory reaction on the part of the thyroid follicles.

Small areas of round-celled infiltration in the thyroid, adrenal, liver, lung, bladder, tongue, rectum and skin.

Reviewing the findings in this case we find that the usual lesions observed in pellagra have been found here with the addition of striking changes observed in the thyroid and adrenals.

As far as the writer is able to determine, no such changes have been found in pellagrins. These changes in themselves would not be especially important if it could be found that careful microscopical examination of these organs had been frequently made in pellagrous individuals. The lesions take on added significance when we review the symptoms and signs of the disease. Even from our as yet incomplete and vague knowledge of the functions and relations of the ductless glands, we do not find it hard to reason on the basis of observed facts in other conditions, that such a syndrome as mental disturbance, cutaneous sensitization to injury by light or other injury, and gastrointestinal disturbance, might very well be secondary to functional disturbance in the thyroid and adrenal. Whether or not other autopsies made on the bodies of pellagrins will show these findings to be of constant occurrence or merely concomitant accidents due to some other primary cause, is a matter for further experience to decide.

There have been clinical reports of cases of pellagra in which the symptoms and signs suggested disease of the thyroid, adrenal, or parathyroid. Beeson reports a case giving evidence of thyroid disease, the signs of which were worse during the attacks of pellagra. Bertelli has recorded a case showing an Addisonian syndrome judging from the title of the paper, the original not being available to the writer. Paravicini has recorded a case of paralysis agitans associated with pellagra. This communication is also not available to me and has been read by title only.

An interesting finding recorded by several writers but especially reported lately by Hillman and Schulle is the lymphocytosis. This finding becomes doubly interesting in view of the thyroid changes found in this instance, since the occurrence of lymphocytosis in hyperthyroidism is well known.

The present case of course throws no direct light upon the question of whether pellagra is an infection of some form of toxic disturbance.

The impression which one gets from a careful perusal of the previous writ-

ings on the pathology of pellagra is that it requires quite a stretch of the imagination to reconcile the findings with an infectious disease. On the other hand, when we remember the psychoses of toxic origin, the gastrointestinal disturbances of toxic origin (either from vagus neuritis or from an effort on the part of the gastrointestinal tract to excrete the poison) and the toxic dermatoses, we find no a priori difficulty in reconciling the disease complex which we call pellagra with a toxic cause. In the light of the present findings we could imagine that this toxic state primarily injured the thyroid and adrenal and that some of the signs and symptoms of the disease as we know it are the secondary results of deranged gland function. It remains of course for further study to determine these points. One thing seems to the writer to be significant; namely, that the changes found in the thyroid and adrenal are unusual ones, thus lending support to the tendency to consider them of importance in the production of the clinical state presented by the patient.

I believe that the nervous lesions hitherto described and partially confirmed by my findings are wholly of toxic or nutritional origin. Many of the lesions to which much space has been given are surely postmortem changes and other artefacts, along with secondary changes which are common in many other conditions. The writer believes that reports of degenerations based upon the appearance of granules and other slight changes in nerve-cells have to be interpreted with extreme caution, inasmuch as so much depends upon the functional state of the cells at the time of death, postmortem change, fixative, method of preparation, etc. One of the safest criteria for the establishment of the fact of nerve cell degeneration is fat, none of which was demonstrable in my case. The nervous findings are being worked up separately with these ideas in mind.

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THE ANTAGONISTIC ACTION OF THE VAGUS AND SYMPATHETIC DIVISIONS OF THE AUTONOMIC NERVOUS SYSTEM IN PULMONARY TUBERCULOSIS.

By Francis M. Pottenger, M.D., Monrovia, Cal.

FOR a number of years I have interested myself in the study of reflex action as it affects the individual suffering from inflammation of the pulmonary parenchyma, particularly tuberculosis. This study has been difficult because of the fact that its very foundation is enveloped in mystery. In offering an explanation of the various phenomena noted, we are compelled to reason from effect to cause in a great many instances, because physiology has not yet made the paths of all the reflexes clear.

This study lies largely within the field of the autonomic nervous system, a field which is particularly characterized by our lack of knowledge, but one which offers great encouragement for future investigations.

The tuberculous patient cannot be understood clinically if we look upon him only as one afflicted with an infection of the pulmonary parenchyma, no matter how small the lesion. We must endeavor to know how the inflammation in the lung affects other organs which are supplied by the same system of nerves or which stand in such a relationship that they may be influenced reflexly; and we must study him as a human being suffering from a chronic disease which produces a chronic toxemia and one which is accompanied by a varied emotional state, both of which conditions exert a powerful influence upon the sympathetic nervous system. Realizing fully the difficulty of the task before me I shall endeavor to suggest some of the symptoms and conditions which arise from the irritation of the two great divisions of the autonomic system, the vagus and the sympathetic, and show the antagonistic action which is constantly going on.

I have been greatly stimulated in this study by the splendid work of Eppinger and Hesz on Vagotonia ("Die Vagotonie," Sammlung. Klinischer Abhandlungen, von Noorden. Heft 9 u. 10, 1910) which has recently come into my hands, and those valuable and suggestive monographs by Cannon ("Bodily Changes in Pain, Hunger, Fear and Rage," Appleton, 1915) on the effect of emotions upon the human organism, and the studies of Beidl ("Innere Sekretion," Urban and Schwartzenberg, Wien, 1910) on the internal secretions.

The autonomic nervous system supplies impulses to structures which are not controlled by the will. These are the organs which are supplied by smooth muscles, such as the stomach, intestines, blood vessels, ducts of glands, skin and secreting glands; also certain organs possessing striated muscle fibres, such as the heart, the beginning and terminal portions of the alimentary canal, and the generative organs.

This system is characterized by the fact that under no circumstances do organs or parts receive innervation directly from a neuron whose cell bodies lie in the brain or spinal cord. Ganglia are interposed between the nerve cells in the central nervous system and the part innervated which act most prob-

ably by modifying impulses. In these ganglia are cell bodies belonging to neurons which have postganglionic fibres which go to supply the viscera.

The cerebrospinal nervous system, on the other hand, is controlled by the will. Its action is quick and definite. There are no ganglia interposed along the path of the nerve to modify the impulses which originate in the brain, but they are carried directly from cell bodies in the brain and cord to the muscles involved, and immediate action results.

The autonomic system consists of three divisions, the cranial, the thoracicolumbar or sympathetic, and the sacral, as shown in Fig. 1 taken from Cannon. No connecting neurons for the autonomic system are given off from those portions of the cord which send out nerves to the fore and hind limbs.

Some writers divide the autonomic system into two divisions, and classify the cranial, bulbar and sacral divisions together as the vagus system, and the thoracic and upper lumbar as the sympathetic system.

The fibres of the sympathetic all pass through the ganglionated cord, while those which come from the cranial, bulbar and sacral portions of the cord do not.

The cranial fibres pass for the most part within the trunk of the nervus oculomotorius (III cranial), are interrupted in the ciliary ganglion, whence they furnish constrictor impulses to the sphincter of the iris.

The bulbar portion passes through the nervus facialis (VII cranial) and nervus glossopharyngeus (IX cranial) to the salivary glands and blood vessels of the mouth. Stimulation causes increased salivary flow in the one case and constriction of the vessels of the mouth in the other.

The most important branch of the autonomic coming from the bulbar portion of the cord is the nervus vagus (X cranial) which is the chief source of nerve supply for the internal viscera. It supplies the heart, bronchial tree, esophagus, stomach, intestines, pancreas, and liver.

The sacral branch is the nervus pelvicus. It innervates the descending colon, sigmoid, anus, bladder and generative organs.

The sympathetic fibres pass from the spinal canal in the thoracic and upper lumbar regions. They pass out and form the ganglionated cord and from this are widely distributed throughout the entire body. Many structures are innervated by both the vagus and the sympathetic systems, and wherever this double innervation is found, the action of the two is antagonistic; as in the eye, where the vagus contracts the pupil, the sympathetic dilates it; or in the heart—where the vagus slows, the sympathetic accelerates.

The cranial and sacral divisions of the autonomic system have a more direct action than the sympathetic because the fibres coming from the cranial and sacral divisions run more directly to the organs innervated than do those of the sympathetic. Thus, the fibres of the vagus supplying the heart and gastrointestinal tract do not enter ganglia until they reach the substance of the organs, while the sympathetic fibres pass through several ganglia each of which complicates and modifies their action. Consequently, stimulation of the cranial, bulbar, and sacral fibres of the autonomic system may cause a resultant action in some individual organ, while stimulation of the sympathetic fibres causes a widespread effect involving several or many organs. This affords us a physio-

logical explanation for the general widespread character of sympathetic impulses.

The following table shows the antagonistic action between the vagus and sympathetic systems in the principal structures concerned in our study:

Action of the Sympathetics When Stimulated.	Organ	Action of the Autonomic When Stimulated.
I-II thoracic	dilates pupil	
	contracts pupil	III N.
I-III thoracic	stimulates orbital muscle	
	stimulates m. ciliaris	III N.
II-IV thoracic	inhibits salivary secretion	
	stimulates salivary secretion.....	Chorda tympani
II-IV thoracic	contracts vessels of skin of head and vessels of brain	
	dilates vessels of brain.....	X N.
	contracts vessels of cheek.....	IX N.
*II Th.-IV L.....	contracts intestinal vessels	
I-IV lumbar	contracts genital vessels	
	dilates genital vessels.....	N. pelvicus
II Th.-IV L.....	stimulates sweat glands	
IV-VII Th.	stimulates hair muscles of face and head	
I-V Th.	accelerates heart contractions	
	slows heart contractions.....	N. X
II-IV Th.	relaxes oesophagus	
	contracts oesophagus	N. X
II Th.-IV L.	relaxes cardia	
	contracts cardia	N. X
II Th.-IV L.	diminishes gastric tonus	
	increases gastric tonus.....	N. X
II Th.-IV L.	inhibits gastric peristalsis	
	increases gastric peristalsis.....	N. X
II Th.-IV L.	diminishes gastric secretion	
	increases gastric secretion	N. X
II Th.-IV L.	inhibits motility of small intestine	
	stimulates motility of small intestine....	N. X
II Th.-IV L.	inhibits (?) pancreas secretion	
	stimulates pancreas secretion.....	N. X
I-IV L.	relaxes contraction of colon	
	stimulates contraction of colon.....	N. pelvicus
I-IV L.	relaxes sphincter ani	
	stimulates sphincter ani.....	N. pelvicus
	stimulates liver secretion	N. X
II Th.-IV L.	contracts and dilates vessels of upper and lower extremities.	

*Th.—thoracic. L. Lumbar.

The vagus system takes part in many reflex acts. The sympathetic also carries afferent impulses, when its end fibres in any organ are irritated, which result in reflex action; and, besides, the system as a whole, is influenced greatly by toxic conditions and by emotional states such as fear, anxiety, discouragement and disappointment.

In pulmonary tuberculosis it can readily be seen that we have a most complex study. There is primarily an inflammation of tissue which irritates filaments belonging to one of the chief branches of the vagus system. Resulting from this, afferent impulses are sent to the cell bodies in the central nervous system and are there transmitted to other cells and through them to fibres which pass out through other branches of the vagus system to produce increased vagus tone in the fibres affected. This increased vagus tone may be distributed more or less generally through the different branches of the vagus system or it may be selective in that it affects certain branches more than others.

Along with the vagus stimulation resulting in increase in vagus tonus, there is a stimulation of the sympathetics, which results in a reflex increase in sympathetic tonus in practically the same organs. Whether sympathetic or vagus tonus shall predominate depends on the conditions present. Cannon has demonstrated the effect of fear, rage and pain on the organism. In tuberculosis we have a central stimulation of sympathetics by the toxins and an exaggerated emotional state, as a result of the disease which also acts as a stimulant upon the sympathetics. Allied to fear and rage are malaise and depressive nervous states which accompany the tuberculous toxemia and which, acting through the sympathetics, have a general antagonistic action to vagus impulses wherever met.

In this connection it is interesting to note how closely the emotional states and toxemias (in this case tuberculous toxemia) are allied in their symptomatology and end effects. The individual in a state of great emotion, shows dilatation of the pupil, pallor, feels his hairs rise on end, suffers from dryness of the mouth, rapid pulse, a stoppage of digestion and other similar symptoms which are characteristic of sympathetic irritation. The toxemia which accompanies tuberculosis, the same as all other toxemias, produces general sympathetic stimulation. The nervous condition resulting is characterized by malaise, anxiety, discouragement, fear and general depression; and these, in turn, cause the same chain of symptoms, only not so pronounced, as a rule, as those which follow violent emotion. Such patients, however, during the periods of marked toxemia, suffer from pallor, rapid pulse, dry mouth, coated tongue, disturbed appetite, slowness of digestion and stasis of intestinal contents. During slight toxemia these symptoms may not be noticed or they may be very slight in character. The symptom-complex of toxemia is an expression of general discharge through the sympathetic nervous system, and is practically the same, though different in degree, no matter what the nature of the toxemia.

The action of the sympathetic on the sacral division is also evident in toxemia as shown in the inhibition of the sexual desire. It is not at all impossible that the increased desire which so often marks periods of improvement in tuberculosis is evidence of increased sacral tonus, and an overbalancing of the equilibrium normally maintained between the sacral and the sympathetic. Inasmuch as these changes in this division of the autonomic system are not so im-

portant in symptomatology as those in the vagus system we shall not discuss them further at this time.

The above symptoms are not constantly present. Variability characterizes the symptoms produced by nervous stimulation in early tuberculosis. This is due to the fact that several important and antagonistic influences are operative at the same time; and also to the fact that the tuberculous inflammation in the lung goes through cycles of greater and lesser activity, producing varying degrees of stimulation; and, further, to the fact that the relative vagus and sympathetic tonus differs in different individuals.

The nerve endings of both the vagus and sympathetic systems are irritated by the pulmonary inflammation; and through their respective fibres afferent impulses are sent centralwards, which result in reflex stimulation of other branches of their respective systems or of nerves with which they communicate, going out to supply such other organs as the eye, heart and gastrointestinal tract. Sometimes the stimulation is greater in the vagus system; at other times in the sympathetic. As a rule, however, except during the periods of increased toxemia, which I shall discuss later, my observation leads me to believe that the vagus tonus is greater than the sympathetic tonus in the majority of patients suffering from early tuberculosis. This seems to be true in nearly all except those of the distinctly asthenic type. This is shown on the part of the heart and particularly on the part of the gastrointestinal tract, as described later.

In estimating the relative tonus of the vagus and sympathetic systems it is necessary to bear in mind that increased tonus might show in one division of nerves and not in all; and that this increased tonus in particular divisions might not be constant. This variability is due to the fact that there are many factors causing the stimulation and that some of these have selective action for certain structures. This is not only evident in the reflexes, but also in the internal secretions which affect the two systems. It is also evident from the fact that the tuberculous patient may have increased or decreased tonus in either the vagus or sympathetic systems from causes other than those which operate as a result of the pulmonary infection. From the antagonistic action of the vagus and sympathetic systems the function of many organs is rendered unstable. The heart particularly in early and nonactive tuberculosis while at rest, is often slower than normal; but on exertion or during periods of emotion at once becomes more rapid than normal and settles down to the normal much slower than it should. The appetite, while disturbed during acute toxic states and during conditions which favor increased absorption of toxins, such as overexertion, or during periods of anxiety and discouragement, is often normal and even sharper than normal when the patient is put at rest in the open air under favorable circumstances which offer him hope of cure. The same is true of the gastric and intestinal disturbances. Hyperacidity and hypermotility are the rule in early tuberculosis, when toxemia is relieved. The intestinal tract also shows the same increased tonus. The vagus system, the one which conserves the healthful action of the important internal organs, overcomes its antagonist in early tuberculosis for the most of the time and thus offers the patient an increased opportunity for restoration to health.

During the waves of increased activity in the tuberculous focus, however,

and when the patient is causing increased absorption of toxins by overexertion and other faulty habits, likewise during periods of discouragement and mental depression, which are not uncommon, the excessive stimulation of the sympathetic system produced by both reflex action, and the toxemia and emotional states, overcomes the increased vagus tonus and causes symptoms which are characteristic of sympathetic irritation, such as rapid heart, decreased appetite, hypochlorhydria, deficient gastric motility and alteration in the secretion and motility of the intestinal tract. Whether this is wholly a direct action upon the sympathetic system or partly a general disturbance of internal secretions is not clear, but the effect is that of a general discharge through the sympathetic system.

The extent to which the sympathetic tonus can be relieved is a factor in prognosis. As the disease increases in virulence and activity, the vagus tonus gradually yields to the supremacy of the sympathetic.

Aside from the antagonistic action of these two systems it seems well established that antagonistic fibres are at times supplied to organs by the same system.

In health a state of equilibrium is maintained in the various organs as a result of the antagonistic action of these two systems. In any disease which affects either by stimulation or by setting aside the normal nerve tonus of any important branch or group of fibres of either or both of these systems, there is a consequent disturbance of equilibrium which results in a pathological state.

This is evident in the production of nausea through eye strain, or the slowing of the heart in abdominal lesions which affect the depressor fibres of the vagus. So it is evident in pulmonary inflammation.

Aside from the direct stimulation of the nerves by inflammatory processes we must recognize the influence of substances of a chemical nature which act either upon terminal filaments or nerve centers. The primary action of the toxins is a direct stimulation. The secondary action may be a totally different one and depend on certain secretions (hormones) which are set free as a result of the primary toxic influence, such as occurs when adrenalin is set free by certain emotional states or gastric secretion is stimulated by the small or taste of savory food.

It is more and more believed as we study deeper into the problems of physiology, that the harmonious and dysharmonious action of cells and special groups of cells is increased not only by direct nerve stimulation, but also by internal secretions which, coming from some distant gland, act as hormones or messengers calling forth normal harmonious action when the parts are in a normal state, and abnormal action when the parts are abnormal. Such action is on the organ itself and not on the nerve supplying it.

This is evident in case of the thyroid, suprarenals, pituitary body, testicles and ovary; and probably just as true in the case of such other organs as the kidney, liver, spleen, pancreas and even such secreting glands as those in the gastrointestinal tract. A dysfunction of one gland may be followed by a disturbance in others because of a failure of the normal secretion of that gland to course in the blood and produce its relative stimulation of other glands. The stimulation of these glands which results in the production of such hormones is at least partially under direct nerve control; and, in this manner, the stim-

ulation of a nerve supplying a given organ may not only affect that particular organ, but one widely separated from it through the internal secretion which is affected by such stimulation.

No doubt future study will clarify this subject very much by the discovery of the true relationship which exists between many of the internal secretions and the structures controlled by them. An important beginning has been made in this direction in the discovery of the fact that the secretion of adrenin is stimulated by the same conditions (emotional states) which stimulate the sympathetic nervous system (Cannon), and that when this substance is thrown out into the circulation, it finds its way to the various structures controlled by the sympathetic nervous system and exerts for the most part, the same antagonistic action against the vagus as the sympathetic itself. This may partly explain the action of toxemia as well as a central stimulation of the sympathetic neurons. There are doubtless other organs which produce hormones antagonistic to sympathetic action; in fact, the observation that dogs whose pancreas are removed have an overstimulation of the adrenal system indicates that such a hormone is produced in the pancreas.

Let us now proceed to apply these principles to pulmonary tuberculosis and the explanation of such phenomena as are caused by the disturbed balance in the vagus and sympathetic systems.

In tuberculosis we must conceive of a condition in which both the vagus and sympathetic systems are simultaneously stimulated, but one in which either one or the other usually yields with a resultant disturbed equilibrium.

Pupil. At least fifty per cent of tuberculous patients show a dilated pupil on the side of involvement during the time that the inflammation is acute; and it is probable that a much larger per cent would show it if observation could be made continuously. This indicates that the action of the sympathetic overcomes that of the vagus. This dilator effect is due to irritation of the fibres from the Ist and IInd thoracic segments of the cord. Artificial stimulation of these fibres causes the same dilator effect. Aside from the pupilary effect, the equilibrium of the ciliary body and orbital muscle is disturbed. I am led to believe, that, aside from the dilatation of the pupil, there is a serious disturbance in the muscle balance resulting from the antagonistic action of the vagus and sympathetic which causes a disturbance of accommodation. It is surprising to see how many patients complain of headache, if they continue to use their eyes for reading, knitting, or sewing, as they have been accustomed to do prior to their illness. They also seem to show an increased and abnormal sensitiveness to bright light; and I often find it necessary to suggest that the bed be so placed that the light will not shine directly in the eyes. Change of eye glasses is made necessary more often than prior to illness even in early and chronic cases which are only slightly active. This is usually explained as being due to the lowered physical state; but may not this altered muscle balance be the cause?

Hectic flush. The vasoconstrictor fibres of the cervical sympathetics take their origin from the upper thoracic roots, particularly from the IId, IIId and IVth, and supply the vessels of the face and head. Hectic flush is present, for the most part, only during periods of acute toxemia, and comes on only after a considerable amount of tissue is involved. It is confined to the side affected,

the same as is noted in the reflex dilatations of the pupil. This of itself suggests that reflex action is at least the localizing factor, although the toxic action may also be required to overcome the constrictor effect.

Heart. In the heart, in tuberculosis, we have so many conditions present which influence the pulse rate that it is impossible to accurately ascribe to the vagus and sympathetic systems the part which each plays. Impulses are carried through both systems, because both are more or less constantly irritated.

As a result of this double source of impulses, the one through the vagus tending to slow the heart, the other through the sympathetic, attempting to quicken its action, there is a marked disturbance in equilibrium. This shows early in the disease before such conditions as loss of pulmonary tissue, heart strain, and degenerative changes can be considered. The heart beat may be normal, or only slightly faster than normal, while the patient is at rest; but unduly rapid on exertion. Rapidity is also increased during states of toxemia and during periods of depression.

This characteristic relative slowness of the heart beat while at rest is sometimes noticed even during periods of temperature in advanced tuberculosis. When compared with the pulse rate accompanying the same degree of temperature in other diseases it is often lower. This is most probably a result of an inhibitory reflex through the vagus, the impulse coming from the irritation in the lung. When the intestinal tract is affected with tuberculosis, then another division of the great vagus system is stimulated and we often see this inhibitory action accentuated, with a still greater departure in pulse rate from that which would be expected with the degree of temperature present. If an unusual slowing of the pulse occurs in the course of pulmonary tuberculosis coincident with an elevation of one or two degrees in the temperature curve, reflex vagus irritation should be considered as a probable cause and a complicating intestinal tuberculosis be suspected.

Irritation of other branches of the vagus will also cause inhibitory action upon the heart. Thus pressing upon the eyeball and irritating the nasal mucous membrane will both cause slowing of the heart; so does intracranial pressure as shown at times in tumors and conditions accompanied by fluid.

Opposing this inhibitory action through the vagus, we have acceleration through the sympathetic, either by direct stimulation, or through toxins or through the various emotional states which affect the patient. Often the sympathetic irritation gains the upper hand and a markedly rapid pulse results.

Gastrointestinal tract. The antagonistic action of the vagus and sympathetic on the different portions of the intestinal tract is extremely interesting; and our understanding of this action will aid greatly in forming an accurate clinical conception of the digestive capabilities of the tuberculous patient.

Early in tuberculosis the toxemia present is neither constant nor of a high degree as mentioned above, and its action upon the sympathetic is negligible as compared with that present in the more advanced cases. From the very first, however, vagus stimulation seems to be important. This is shown in the larynx, in hoarseness due to interference with the innervation, and also in the irritation which produces cough. It is likewise marked in the intestinal tract, as I shall now describe.

Increased salivary flow. This is present at times in tuberculous patients, though by no means constant. This could be due to reflex stimulation of the salivary glands through the vagus branch which courses with the chorda tympani. The dry mouth and coated tongue are almost always present during the periods of toxemia, and, at times, when this has passed away. This is an expression of increased sympathetic action.

Coated Tongue. A dry coating of the tongue is often noticed during periods of temperature in cases where toxemia is a factor. The drying effect on the secretions through the sympathetics must be thought of as an etiological factor. The fact that this is nearly always accompanied by a diminution of appetite and deficiency in gastric and intestinal efficiency makes the cause the more probable, for these other conditions are likewise due to deficient vagus tonus or increased sympathetic tonus.

Stomach. The disturbance on the part of the stomach in early tuberculosis, except during periods of acute toxemia and periods of depression are those which belong to the class of so-called nervous dyspepsias. The form which seems most common is a slight hyperacidity. This may be brought about by a reflex through the vagus, the impulse coming from the inflamed pulmonary parenchyma. The digestive powers are, if anything, above par. This may be a reason why the tuberculous patient at these times is able to care for such large amounts of food. Associated with the increased secretion there is also an increased motility and at times, a spastic constipation. This increased vagus tonus sometimes shows itself in a feeling which approaches nausea. These conditions, however, are not continuous. They alternate with decreased vagus tonus as mentioned above. This increased vagus tonus can be relieved by the administration of atropin, and following its administration hyperacidity and hypermotility often disappear. There are several factors which come in to cause sympathetic stimulation and inhibition of vagus action, notably reflex irritation, the toxemia and the depressed nervous state which is so common and which is characterized by mental depression, anxiety, discouragement and fear. These emotional states come and go all through the disease. They are sometimes dependent upon and sometimes independent of toxemia.

Intestines. A similar condition obtains in the intestinal tract where we have states of increased vagus tonus, causing increased secretion and increased motility, and abnormal sympathetic irritation inhibiting this and interfering with secretion and peristaltic action. Spastic constipation as a result of increased vagus tonus is common in early tuberculosis, while the atonic type is the rule later. Definite effects of each system are not so easy to point out in the intestinal tract because of the preponderance of stasis and constipation, which are regularly found in general life and which affect so many of those who are afflicted with tuberculosis prior to the time when the disease becomes manifest. We can say, however, that, as a rule, digestion becomes impaired and stasis and constipation become more pronounced as the disease advances and toxemia and the various depressive emotional states become more marked.

Thus, it would seem that early tuberculosis is largely a condition in which increased vagus tonus predominates over sympathetic stimulation, and advanced

tuberculosis a condition in which sympathetic irritation seems to be greater than the vagus tonus.

In offering this analysis of nervous action in tuberculosis, I realize fully that it is impossible to always point out the direct relationship between cause and effect; because we are dealing with a disease which produces dysfunction on the part of many organs and which results in a multitude of conditions which might produce symptoms similar to those which could be explained at one time by irritation of the sympathetics, at another by irritation of the vagus. It can be seen, however, that these two systems are to be taken into account, and that, as long as inflammation in the lung exists, so long are impulses carried to various organs through these two systems, which, acting antagonistically, disturb the normal equilibrium, which is so necessary to normal function.

ETIOLOGY AND LABORATORY DIAGNOSIS OF SMALLPOX AND CHICKENPOX*

By J. N. Force, M.D., Berkeley, Cal.

ELEVEN years after Jenner published his monograph on vaccination, Sacco recorded the presence of granules in the lymph contained in the vaccine vesicle, but it was not until 1868, however, that Chauveau[1] was able to show by diffusion experiments, that the active principle of vaccine virus was contained in these granules and not in the fluid in which they were suspended.

Beginning with Cohn[2] in 1872, a number of observers made careful studies of the bacteria found in the vaccine vesicle, but no one was able to produce the lesions of vaccinia by means of animal inoculation with a pure culture of any one of these bacteria.

De Waele and Sugg[3] during a smallpox epidemic succeeded in isolating from the blood of persons dead of the disease, a streptococcus which was agglutinated by the serum of smallpox cases in dilutions of 1 in 800. The same organism was isolated from the vesicles of vaccinia cases and was agglutinated by the blood of other vaccinia cases. These same observers[4] isolated a streptococcus from chickenpox vesicles which, though readily agglutinated by the serum of chickenpox cases, was not agglutinated by the serum of smallpox cases, vaccinia cases, or new-born infants. After a large number of control experiments with other streptococci, de Waele and Sugg announced the specificity of these streptococci and suggested the agglutination test as a means for the differential diagnosis of smallpox and chickenpox. It is indeed remarkable that so definite a statement involving both morphology and immunology of supposed causative agents for these two diseases should be neither confirmed nor denied by other observers. It is possible that the scientific world hesitated to recognize streptococcus variolæ until specific immunity had been produced in animals by inoculation with a pure culture of the newly discovered organism.

The failure to produce vaccinia with any bacteria contained in the vaccine vesicle naturally suggested that these bacteria were in the nature of secondary

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invaders and led to a desire to see how the vaccine lymph would behave if free from this contamination. Cheyne[5] in 1850 suggested the use of vaccine virus mixed with glycerin as a substitute for the dry point, though this suggestion was made in the interest of convenience of handling and preservation rather than removing contamination. Copeman[6] in 1891 showed that vaccine virus mixed with fifty per cent glycerin would retain its activity even though the bacterial content of the mixture gradually lessened. The following year Chambon, Menard, and Straus[7] came to the same conclusion independently since they were able to produce typical vaccinia lesions with a mixture of virus and glycerin sixty days old. The mixture was entirely free from the usual bacteria as was shown by plating experiments.

The fact that typical vaccine vesicles could be produced by a bacteria free virus suggested a protozoan origin for the disease. Guarnieri[8] in 1892 gave the name cytoryctes to certain bodies which he found constantly occurring in the epithelial cells of smallpox vesicles as well as in the corneal epithelial cells of rabbits fifty hours after inoculation of the cornea with vaccine virus. These bodies were extranuclear in the epithelial cells and varied in shape and size, being on the average half the size of the cell nucleas. Councilman, Brinckerhoff, and Tyzzer[9] believed that the bodies or cytoryctes of Guarnieri were the true parasites of smallpox and vaccinia. They also described a second form which was present within the nucleus of the epithelial cell in smallpox only. They considered the forms to represent two stages in the life history of the same organism and ascribed the differences between variola inoculata and vaccinia in monkeys to the presence of the intranuclear form in the former disease. The intranuclear forms were most abundant in the vesicles of a general eruption produced by the intravenous inoculation of smallpox virus, but were only occasionally found in the lesions produced by skin inoculation of the same virus. The extranuclear forms or original cytoryctes were present in both smallpox and vaccinia lesions.

In connection with the above studies, Tyzzer[10] carried on an independent investigation of the histology of the chickenpox vesicle. Though unable to produce any reaction in the corneal epithelial cells of a rabbit or in the skin of a monkey by inoculation with chickenpox vesicle contents, he described certain bodies enclosed in the nuclei and cytoplasm of the epithelial cells of the chickenpox vesicle. Associated with appearance of these bodies is a division of the nucleus and an enlargement of the epithelial cells. The resulting large polynuclear cells, Tyzzer considered characteristic of chickenpox. He did not consider the inclusion bodies parasitic in character nor did he think that they would be confused with cytoryctes by an experienced observer. The inability of Tyzzer to produce lesions with chickenpox material in the corneal cells of rabbits was in the nature of a confirmation of the observations of Salmon[11] who was unable to affect the cornea with either chickenpox or confluent acne material, though finding it easily affected by both smallpox and vaccine virus.

The newly discovered cytoryctes were not universally accepted as the causative agent of smallpox. In the year following the publication of Guarnieri's discovery we find Ferroni and Massai[12] expressing a belief that Guarnieri's parasites were irritation bodies derived from the nuclei of the epithelial cells.

This belief was based on corneal inoculations with croton oil and india ink. Resulting stained sections showed bodies practically identical with the cytoryctes. Further confirmation of the nonparasitic character of these bodies was offered by Salmon[13] who showed that the staining reactions of the parasites, while differing from those of the nucleus of the epithelial cell, corresponded to those of the nuclei of migrating leucocytes whose chromatin masses tend to break down in the invaded cells. Foa[14] also denied the parasitic nature of the cytoryctes on the ground of a nonprotozoan morphology, the resistance of vaccine virus to physical and chemical agents capable of destroying the cytoryctes, and finally that analogous forms found in sheep-pox will not traverse the filter which allows passage of the sheep-pox virus. Von Prowazek[15] discovered that the young cytoryctes were tied by filaments to the cell nucleus. He did not consider them parasites, products of degeneration, or even the nuclei of wandering leucocytes, but rather a hyperproduction of nuclear material on the part of the epithelial cell as a reaction to stimulation produced by the smallpox organism. He believed that the extruded nuclear material surrounded the organism and suggested the group name chlamydozoa (chlamys, a cloak) for all organisms causing similar reactions. He admitted that bodies resembling cytoryctes could be produced by the irritation of the cornea with various substances, e. g., trypsin, but held that the production of true cytoryctes was a specific property of the smallpox organism. Finally he showed that cytoryctes could not be produced in the corneal cells of rabbits by inoculation with heated vaccine virus, though the same heated virus would produce immunity if injected subcutaneously.

It has been stated above that Tyzzer noted inclusion bodies in the epithelial cells of the chickenpox vesicle. He did not consider these parasitic, was unable to produce them in corneal lesions, and did not consider them readily confused with the cytoryctes. On the other hand Keysselitz and Mayer[16] believed the chickenpox inclusion bodies to be analogous to the cytoryctes though they believed that the actual organism of chickenpox is located within the inclusion bodies, thus following the chlamydozoa theory of von Prowazek. Bertarelli[17] was unable to inoculate either child, monkey, dog, or guinea-pig with chickenpox vesicle contents or dried crusts. He did, however, in contradistinction to Tyzzer, succeed in producing a corneal reaction in rabbits which was characterized by inclusion bodies in the epithelial cells. The bodies were not as large or as deeply stained as the cytoryctes, but they were not confusable with the irritation forms produced by osmic acid or bacterial toxins. Swellengrebel[18] confirmed the observation of Bertarelli concerning the staining characters of the chickenpox inclusion bodies. He differentiated them from the cytoryctes by a structure more like the nucleus in character, and a location more often within the nucleus of the epithelial cell, though these differences were not at all constant.

Aside from the corneal inoculations with chickenpox vesicle contents, the only results of inoculation which seem to be beyond question are those of Kling.[19] Kling easily inoculated healthy children by pricking the skin of the arm with a lancet charged with fluid from a fresh chickenpox vesicle. At the end of eight days, a typical chickenpox vesicle appeared, which was transmitted for five passages. The vesicle appeared in children recently vaccinated against small-

pox which shows that the lesion produced was not due to vaccinia. Out of thirty-one children inoculated in this manner during an epidemic in a children's hospital, only one had a febrile attack of chickenpox. In the same hospital there were thirty-two cases of chickenpox out of sixty-four unvaricellated children. Rabinoff[39] has recently applied the varicellation method of Kling to seventy-six children in an infant asylum. The six cases of chickenpox which appeared in this group all occurred within ten days after varicellation, i. e., within the incubation period of the disease. Out of one hundred and forty-two susceptible children in the same asylum, there were one hundred and fourteen cases of chickenpox. These figures represent an incidence of eight per cent in varicellated cases as against seventy-five per cent in susceptible cases.

These observations of Kling in conjunction with the findings of Bertarelli and Swellengrebel show that the clinical similarity of chickenpox and mild smallpox is confirmed by a similarity of the reaction of the epithelial cell to the invasion of either organism, as well as a similarity in the protection afforded by both vaccination and varicellation. On the other hand, the fact that a smallpox immune child could be varicellated indicates that the two diseases are not modifications of the same process as believed by Hebra.

It is needless to say that while the studies on cytoryctes were in progress, many attempts were made to pass the smallpox organism through the Berkefeld filter. All these experiments resulted in failure until Nicolle and Adil-Bey[20] in 1900 passed vaccine virus through the filter after a preliminary digestion of the vaccine lymph with pancreatic juice. Negri[21] diluted fresh unglycerinated pulp with ten to twelve times its weight of water and ground it in a mortar. The ground pulp was allowed to stand on ice for several days and then reground in a Csoker grinding machine. The filtrate from the resulting emulsion gave typical corneal reactions including cytoryctes though a large quantity of the filtrate and a ten hour contact with the cornea were necessary. Green[22] collected vaccine pulp, triturated it with saline solution, heated at 60° C. for one hour, and filtered through the Berkefeld filter. The filtrate injected subcutaneously into guinea-pigs, monkeys, and calves produced immunity against subsequent skin vaccination. In a later communication, Green[23] reports inability to produce any trace of vaccinia in calves and guinea-pigs vaccinated with the filtrate of vaccine pulp removed from calves ninety-six hours after vaccination and diluted 1 in 8 with five per cent sodium citrate solution. Foster and Force treated glycerinated vaccine virus with ether, removed the ether, diluted the vaccine virus 1 in 50 with saline solution, and centrifuged at high speed. The supernatant fluid was divided into two portions, one of which being passed through the Berkefeld filter. Guinea-pigs were then inoculated subcutaneously with equal doses of the filtered and unfiltered portions. Subsequent scrotal vaccination of the guinea-pigs produced abortive vesicles where the animals had been inoculated with the filtrate, and distinct allergic reactions where the animals had been vaccinated with the unfiltered supernatant fluid. Repeating the experiment with unetherized virus gave similar results. Control scrotal vaccination with the original virus gave typical vesicle formation.

Experiences in the filtration of vaccine virus indicate that the organism is contained in some type of surrounding substance and is incapable of passing the filter until this substance is removed by digestion, grinding, or the action

of solvents. This is strictly in accord with the chlamydozoa theory of von Prowazek. It is also evident that the activity of the virus is reduced by filtration, whether by mechanical action of the filter, or by inability of the organisms to separate in sufficient quantities from their surrounding cytoryctes. This is shown by the partial protection of guinea-pigs receiving a subcutaneous inoculation of filtrate as contrasted with the complete protection afforded by an equal quantity of ground, centrifuged, but unfiltered vaccine virus. Whatever effect the ether may have had in dissolving the cytoryctes was offset by the marked tendency of the etherized virus to clog the filter.

Von Prowazek gave the name chlamydozoa to organisms characterized by the formation of a surrounding cloak derived from the nucleus of the invaded cell. Fornet[24] suggested the name microsoma to designate the group of pathogenic germs to which belong the bodies described by Flexner and Noguchi in poliomyelitis and rabies, as well as the smallpox organisms. Microsoma variolae, according to Fornet, occur in pairs surrounded by a narrow halo which is easily seen when stained by Giemsa's solution. They are agglutinated completely by the serum of a smallpox case. Volpino[25] under the name of "corpuscles mobiles" described similar bodies seen with the ultramicroscope in the corneal epithelial cells of the rabbit. These bodies do not exceed 0.2 microns in diameter, are very numerous, and very motile. Volpino laid great stress on the diameter of these bodies as distinguished from those described by Paschen[26] which measured 0.5 microns and were contained in fresh lymph taken from a child. Volpino considered these to be leucocytic granules.

The most careful and comprehensive study of the morphology of the smallpox organism is that of Belin.[27] After vaccinating the cornea of a rabbit, he sutured the eyelids together assuming that the tears would rid the site of extraneous organisms and leave a practically pure culture of the smallpox organism. Studies made of the pus resulting from this vaccination showed the following forms against the dark field:

1. Motile coccoid forms less than 0.5 micron in diameter which were agglutinated by the serum of smallpox immunes.
2. Similar forms within the corneal cells.
3. A very few large oval bodies sometimes as large as 2.0 microns.
4. Spirochaetes occurring early, very fragile, and in many cases containing in one end a small body similar to the free coccoid form of the organism.

In a later communication, Belin[28] states that he was able to obtain all these forms from a serum broth to which had been added small particles of rabbit skin inoculated with vaccine virus. Belin claims that reproduction of the organism took place in this culture medium since vaccination on the backs of rabbits with emulsions made from skin particles fished from the broth produced confluent eruption on using particles which had been in the broth four days, where only a few discrete vesicles were produced by using particles which had been in the broth a shorter time. A portion of fourth-day emulsion produced discrete vesicles after being passed through a Berkefeld filter.

The work of Belin furnishes a combined study of morphology and attempts to cultivate the vaccine organism in vitro. Several other reports have been made recently on the cultivation of a bacteria free vaccine both in vivo and in

vitro. Steinhardt, Israeli, and Lambert[29] repeated the work of Belin using fragments of rabbit cornea inoculated with vaccine virus and incubated at 37° C. The incubated corneal fragments gave rise to confluent eruptions on the backs of rabbits, while unincubated controls gave only discrete vesicles. Steinhardt-Harde[30] secured a bacteria-free vaccine by the dialysis of commercial glycerinated virus through collodion sacks. This process removed the glycerin and phenol. The contents of the sacks were either plated on agar or re-dialysed with 0.5 per cent phenol. In the first instance the spaces between the contaminating organisms which appeared on the agar plates were carefully cut out and the vaccine removed therefrom. In the second instance the re-dialysis gave rise to a bacteria-free liquid virus which was much more active than when the bacteria had been killed by shaking with ether as advocated by Fornet. Fornet,[24] however, holds that shaking with ether does not seriously impair the vitality of the virus, since he succeeded in transplanting the organism for seven generations in serum broth to which a piece of sponge platinum had been added. This growth was secured after the removal of contaminating bacteria by means of ether. Fornet was able to vaccinate a calf with the seventh generation broth culture and is convinced that this result was not due to dilution of the original material, since this would represent a dilution of 1 in 1,000 billion even in the fifth generation which is considerably beyond the limits of activity of diluted vaccine virus. Fornet's studies on the morphology of the organism agree in the main with those of Belin, Prowazek, and Volpino. Fornet's method of securing a bacteria-free vaccine virus is believed by Voigt[31] to have little commercial value, since etherized virus will not retain its potency as long as the ordinary glycerinated product, so that whatever is gained by a shortened period between preparation and distribution is lost by a correspondingly shorter period of potency after marketing. Foster[32] secures a marked reduction in the number of bacteria by bubbling ether through a long column of vaccine pulp for a few hours. He does not continue the process until the vaccine is bacteria free, but depends on the glycerin to complete the process during the period of storage which is considerably shortened by this method. This vaccine virus has been in use in the University of California Infirmary for the past year and one hundred per cent of "takes" in previously unvaccinated persons with no history of smallpox testify to its potency. Noguchi[33] has recently succeeded in restoring the virulence of vaccine virus which had been freed from bacteria by etherizing according to the method of Fornet. He inoculates the testicles of rabbits and bulls thereby securing large amounts of protected epithelial surfaces for the propagation of the virus.

A summary of our information regarding the organism of smallpox presents the following points:

1. The organism is present in the lesions of smallpox and vaccinia.
2. The organism is a filterable virus normally occurring as a coccoid form measuring from 0.2 to 0.5 micron in diameter.
3. The organism invades epithelial cells and derives an enveloping substance from the nuclei of these cells.
4. The organism is capable of inoculation in animals though affected somewhat in its general activity by the tissue selected for inoculation or by the portal of entry into the body.

5. It occurs in skin lesions accompanied by bacteria and the removal of the bacteria is difficult of accomplishment without lessening the activity of the organism.

6. The organism has been grown in pure culture in vivo, and in culture media containing epithelial tissue. It has possibly been grown in culture media without epithelial tissue, though this last point needs confirmation.

The organism of chickenpox resembles that of smallpox in its invasion of epithelial cells and the formation of an enveloping substance derived from the nucleus. It has produced inclusion bodies in the corneal epithelial cells of rabbits and has been carried from arm to arm for several generations. Owing to the difficulty of animal inoculation it has never been proved that it would pass through a Berkefeld filter.

Differential Diagnosis of Smallpox.

Much has been written concerning the clinical differences between smallpox and chickenpox, but the fact remains that the morphological similarity of the two organisms is borne out in the diseases produced by them. In every epidemic of smallpox there are so-called "border line" cases which present great difficulty in diagnosis. Smallpox may occur with non-umbilicated vesicles; chickenpox with eruption on the palms and soles, or characterized by definite umbilicated pustules. "One cannot depend absolutely on the gross appearance of the lesion or on its distribution" (Tyzzer). Since the mild cases of smallpox may give rise to severe cases in other individuals, and since our control procedures are radically different for the two diseases, it follows that a laboratory method of diagnosis would be of value to the health officer especially in dispute with physicians unwilling to accept the bedside diagnosis of smallpox.

The following methods of laboratory diagnosis have been suggested at various times:

1. Microscopical examination of the vesicle contents. According to Tyzzer a diagnosis of chickenpox may be made at the bedside by finding the large polynuclear cells which he considers characteristic.

2. Excision of the skin lesion and histological examination. This procedure presupposes a certain degree of familiarity with the not too constant differences in the histology of the invaded epithelial cells. If the diagnosis be made on the basis of inclusion bodies it must not be forgotten that very careful technic is necessary to differentiate these extremely similar bodies.

3. Inoculation of the cornea of a rabbit with the vesicle contents. In this method cover glass preparations may be made directly from the corneal ulcer. The epithelial cells which adhere to the cover glass may be fixed, stained, and examined for inclusion bodies. Paul[34] varies this technic by examining the cornea with a hand lens thirty-six hours after scarification in order to detect "air blisters" characteristic of smallpox. Failing to find these "air blisters" he enucleates the eyeball at the end of forty-eight hours and immerses it in a mixture of mercuric chloride and alcohol. The necrotic spots appear as white circular punctures. Neither the "air blisters" nor the necrotic spots are found when chickenpox material is used. Paul admits that the "air blisters" are easy

to overlook and extremely careful technic must be used in enucleating the eyeball in order to avoid smearing the cornea with blood.

4. The inoculation of a well vaccinated person with the contents of the vesicle. Jenner[35] in his original series of experiments noted that a sudden efflorescence was produced on the application of smallpox material to the scarified skins of persons who had suffered from smallpox, variola inoculata, or vaccinia. Tieche,[36] appreciating the technical difficulties of the usual laboratory diagnosis of smallpox, suggested that these cutaneous allergic phenomena would be present if smallpox vesicle contents were inoculated into the scarified skin of a well vaccinated person, while no result would follow a similar inoculation with chickenpox vesicle contents. Any danger of accidental infection could be overcome by heating the suspected material to 70° C. for five minutes. The fact that Kling had secured typical chickenpox vesicles by arm-to-arm inoculation did not disturb Tieche for, in a later communication,[37] he argued that the chickenpox vesicles did not appear for several days after inoculation while the allergic reaction due to smallpox would appear in twenty-four to forty-eight hours. It would seem that Tieche has overlooked one very important factor in the production of cutaneous allergy. Since the chickenpox organism affects epithelial structures, is contained in the vesicle contents, and can be transmitted from arm to arm, it follows that cutaneous allergic phenomena are theoretically possible in response to the varicellation of a person immune to chickenpox. Therefore, unless Tieche secured persons for his test subjects who had neither had chickenpox nor been varicellated, his observations would be open to confusion.

5. Inoculation of vaccinia immune rabbits with the contents of the vesicle. This method suggested by Force and Beckwith[38] retains the simplicity of the method of Tieche while guarding against the possible error due to the use of human subjects. Since chickenpox has never been transmitted to the skin of a rabbit, repeated inoculation with chickenpox material will not result in allergic reactions. On the other hand, rabbits sensitized by vaccination with vaccine virus will give a marked intradermal reaction with smallpox vesicle contents in from twenty-four to forty-eight hours. The original vaccination may be either cutaneous or subcutaneous and the cutaneous allergy in some rabbits persists over a year. The reaction has been produced with smallpox vesicle contents nine days after removal from the patient which would allow time for transportation to central laboratories where immune animals might be kept. Intradermal inoculation with 0.1 c.c. of a 1 in 10 dilution of smallpox vesicle contents is followed by the appearance within twenty-four hours of an indurated reddened nodule measuring from 10 to 25 m.m. in diameter. The reaction reaches its maximum development in forty-eight hours. In speed, in simplicity, and in the positive character of the results this method should commend itself to the laboratory worker as a substitute for the more exacting technic of inoculation on the rabbit's cornea.

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LABORATORY METHODS

Methods for the Determination of Glucose in the Blood

Method of Shaffer.[1]

FIVE c.c. of blood are withdrawn from an arm vein. A few grains of powdered potassium oxalate are placed in the pipette to prevent clotting, as suggested by Folin and Denis, the tip of the pipette being inserted in the rubber tubing attached to the needle. The blood is run at once into an Erlenmeyer flask of 100 to 200 c.c. capacity containing 25 c.c. of water. The pipette is rinsed out twice with the same water. If duplicate determinations are desired, 10 c.c. of blood are drawn and the amounts of water and the other agents are doubled.

"*The removal of proteins.* For the removal of proteins the flask, covered with a small watch glass, and held at the neck with a test tube holder, is heated quickly over a small flame just to boiling. During the heating the flask should be rotated gently; evaporation is to be avoided. A few drops of dilute acetic acid are at once added to the hot liquid to produce a visible coagulum. Five c.c. of colloidal iron solution (iron dialyzed, Merck) is next added and the mixture well shaken, after which about 0.2 gram of powdered sodium sulphate is added and the mixture again shaken for about ten seconds. The liquid is then poured as completely as possible into a 50 c.c. centrifuge tube and centrifuged at moderate speed for one or two minutes. The water-clear liquid is then poured off through a small filter and 21 c.c. equivalent to 3 c.c. of blood are measured into another 50 c.c. glass centrifuge tube. Twenty-one c.c. of mixed Fehling's-Allihn solution is then added and the tube immersed in boiling water, to the height of the liquid inside the tube, for ten minutes.

"The centrifuge tubes are of rather heavy glass, but are fairly resistant to even such sudden changes of temperature. It is, however, important that they should not be in contact with metallic supports when plunged into the hot water. I have found very satisfactory and convenient for this purpose circular racks, made similar to test tube racks, but constructed of 'fibre board' which is very resistant to the hot water. A rack about 15 c.m. in diameter has space for six tubes and of course permits the heating of all at one time."

"On removal from the water bath the tubes are placed in the centrifuge (each pair being balanced by the addition of water if necessary) and centrifugated for two to four minutes, which packs the cuprous oxide in the bottom of the tube. The liquid is then carefully poured off as completely as possible without loss of oxide. This should be done over a white evaporating dish and in a light place which permits one to see when the oxide is disturbed. The tubes are then partly filled with cold freshly boiled water, the pairs balanced

and once more centrifugated for two or three minutes, after which the wash water is poured off as before. The cuprous oxide may now be determined in either of two ways, both of which are satisfactory.

"Colorimetric determination of cuprous oxide. The sediment of cuprous oxide is dissolved in the smallest possible amount of concentrated nitric acid (2 to 10 drops) and then is diluted with ammonia water (1 part strong NH_4OH to 5 parts water) to such a volume that the blue color is roughly about the same as the standard. Cylinders (10 c.c. to 50 c.c.) may be used for this dilution, though of course the reading of the volume should be accurately made. The unknown is then read against the standard copper solution, the latter set at 20 m.m. in a Duboscq colorimeter.

"The standard ammoniacal copper solution contains 5 mgm. of copper in 10 c.c. and is prepared by dissolving 9.82 grams of crystaline copper sulphate in 500 c.c.; 10 c.c., of this solution is diluted to 100 c.c. with 1 to 5 ammonia, which gives a solution that may be easily and accurately read in the colorimeter. I find it best to set the standard at 20 m.m., though from 10 to 30 m.m. it reads almost equally well. The unknown should be between the limits of from half to twice the color of the standard; within these limits the dilution is without much influence. The amount of copper in the unknown is found from the following formula:

$$\frac{\text{St.} \times 5 \times \text{v}}{\text{R} \times 10} = \text{mgm. Cu. found,}$$

in which St. = reading of standard, R = reading of unknown, and v = volume of unknown.

"This method has been found quick and convenient, though not especially more so than the Bertrand titration as described below. The results agree within 2 or 3 per cent."

"Determination of copper by Bertrand titration. The washed cuprous oxide contained in the centrifuge tube is dissolved by adding about 0.5 c.c. of strong ferric sulphate sulphuric acid solution,[2] and is immediately titrated in the centrifuge tube with $\frac{N}{20}$, $\frac{N}{50}$ or $\frac{N}{100}$ potassium permanganate, depending upon the amount of cuprous oxide present. The small amount of liquid in the tube permits a sharp end-point to the titration even with very dilute permanganate. The permanganate should be freshly prepared from a standardized $\frac{N}{10}$ stock solution. One c.c. of $\frac{N}{10}$ permanganate is equivalent to 6.36 mgm. of copper.

"Corrections and calculation. Practically all preparations of Fehling's solution deposit small amounts of cuprous oxide when heated. Blank determinations of 20 c.c. of Fehling's solution with 20 c.c. of water heated in a boiling water bath for ten minutes usually yield the equivalent of about 1 mgm. of copper. Such blank determinations must be made on the solution used and the amount subtracted as a correction.

"For the conversion of the result in terms of copper into milligrams of glucose the following table is used. The table has been prepared from the results of a large number of determinations of pure glucose solutions. The amount of copper found, minus the correction, divided by the corresponding factor, equals milligrams of glucose in the blood represented by the amount of filtrate used.

For example, 21 c.c. of blood filtrate, representing 3 c.c. of blood, gave a titration of 5.5 c.c. $\frac{N}{10}$ permanganate."

$5.5 \times 1.27 = 6.99 - 1.2$ (Correction) $= 5.79$.
$5.79 \div 2.19 = 2.64$ mgm. glucose or 0.088 per cent in the blood.

TABLE I.

STANDARD COPPER: GLUCOSE VALUES.

20 c.c. of sugar solution plus 20 c.c. Fehling's solution heated 10 minutes in a boiling water bath. Mgm. Cu. — divisor = mgm. glucose.

MGM. COPPER	DIVISOR	MGM. COPPER	DIVISOR	MGM. COPPER	DIVISOR
0.7	1.50	6.0	2.19	20.0	2.06
1.0	1.60	7.0	2.18	25.0	2.04
1.5	1.70	8.0	2.17	30.0	2.03
2.0	1.80	9.0	2.16	35.0	2.01
2.5	1.90	10.0	2.15	40.0	2.00
3.0	2.00	12.0	2.14	50.0	2.00
3.5	2.10	14.0	2.12	60.0	1.99
4.0	2.20	16.0	2.10	80.0	1.98
5.0	2.20	18.0	2.08	100.0	1.97

METHOD OF KOWARSKY AS MODIFIED BY STROUSE.

Strouse, Stein and Wisely have recently reported a modification of the Kowarsky method which requires the use of only 0.5 c.c. of blood for each determination.

SOLUTIONS.

I.	Copper sulphate (pure crystals)	8.0
	Dextrose (C. P.)	0.1
	Water to	200.0
II.	Pure Rochelle salts	40.0
	Sodium hydroxide (sticks)	30.0
	Water to	200.0
III.	Ferric sulphate	10.0
	Concentrated sulphuric acid	40.0
	Water to	200.0
IV.	Potassium permanganate	1.0
	Water to	200.0
V.	Liquor ferri oxidati dialysati (Merck)	5%
VI.	Sodium fluoride	0.2% solution
	Also pulverized Rochelle salts.	

"Solution IV is used in a 10-fold dilution freshly prepared each day. It must first be standardized by titration against oxalic acid. The equivalent of the permanganate solution in copper is obtained by this titration. Kowarsky recommends the following technic of standardization. Exactly 0.1 gm. of ammonium oxalate is dissolved in 100 c.c. of distilled water. To 10 c.c. of this solution 2 c.c. of concentrated sulphuric acid are added. The diluted permanganate solution is now titrated against this oxalic solution to a permanent red reaction. The number of cubic centimeters of permanganate solution is then made the denominator of a fraction of which the constant 8.95 is the numerator. The resulting figure equals the amount of copper in milligrams represented by 1 c.c. of the permanganate solution.

Apparatus Needed.—"1. Several centrifuge tubes of ordinary laboratory size carefully calibrated and marked at the 0.5, 1.0, 5.0 and 10.0 c.c. points. We

have found it advisable to calibrate our own tubes, as several supposedly accurate tubes showed errors as high as 40 per cent.

"2. An ordinary laboratory centrifuge.

"3. Small Erlenmeyer flasks—capacity 50 c.c.

"4. An Allihn filter and suction pump.

"5. Washed asbestos.

"6. Burette of 10 c.c. capacity divided into $\frac{1}{20}$ c.c. (0.05).

"7. Volumetric flasks, 2, 3 and 5 c.c. pipettes, etc., as found in any laboratory.

The Method.—"The sodium fluroide solution is placed in one of the calibrated centrifuge tubes up to the 0.5 c.c. mark. In practically all of our work the blood from a finger or ear prick was allowed to drop into the tube up to the 1 c.c. mark, thus giving exactly 0.5 c.c. blood. Water is then added up to the 5 c.c. mark, a pinch of powdered Rochelle salts dropped in, the whole shaken and allowed to stand until the Rochelle salts are completely dissolved. Then the solution of dialysed iron is added, making the total contents of the tube exactly 10 c.c. It is now corked and vigorously shaken until the originally putty-like mixture becomes homogeneous and fluid. Centrifugalize for 3 to 5 minutes.

"The dialyzed iron-blood mixture when removed from the centrifuge should show a water-clear supernatant fluid. Exactly 5 c.c. of this clear fluid is used in the copper reduction, which is performed by mixing exactly 2 c.c. of each of solutions I and II in the small Erlenmeyer flask and then adding the clear filtrate.

"The reduction process must take place on an asbestos mesh over a low constant flame and must continue exactly 3 minutes from the time boiling starts. While this is going on, the asbestos filter is prepared and washed, and the suction pump thereby tested out. After 3 minutes' boiling the Erlenmeyer is rapidly cooled under the cold water faucet without shaking, and the contents immediately poured on the filter. The reduced copper oxide remains in part adherent to the sides of the Erlenmeyer flask and to the surface of the asbestos filter, and both flask and filter must be carefully washed several times with distilled water.

"The funnel is then disconnected from the filtrate flask containing the unreduced copper sulphate and the washings. The filtrate flask is thoroughly cleansed with distilled water and again connected up with the funnel. Three cubic centimeters of the acid ferric sulphate solution are now added to the original Erlenmeyer flask, care being taken that it is well distributed over the whole of the inside of the flask. The contents of the flask are then poured upon the asbestos in the funnel and allowed to stand one minute. By this time all the reduced copper will have been taken into solution and the suction pump is again started. The Erlenmeyer flask is carefully washed 3 or 4 times with 3 to 5 c.c. of distilled water, each washing being poured into the funnel of the suction pump. The contents of the filtrate flask are then titrated against the permanganate solution diluted 1:10, until a definite pink color persists.

"The results are easily figured. The amount of permanganate solution in cubic centimeters is muliplied by the constant for this solution (as previously

determined) and its equivalent in milligrams of dextrose obtained from the following table.

Copper	Sugar	Copper	Sugar	Copper	Sugar
1.95	1.0	3.50	1.8	5.00	2.6
2.15	1.1	3.70	1.9	5.20	2.7
2.35	1.2	3.85	2.0	5.40	2.8
2.55	1.3	4.05	2.1	5.60	2.9
2.75	1.4	4.25	2.2	5.75	3.0
2.90	1.5	4.45	2.3	5.95	3.1
3.10	1.6	4.65	2.4	6.15	3.2
3.30	1.7	4.80	2.5	6.35	3.3

"But it must be remembered that 200 c.c. of the original copper solution contained 100 mg. of dextrose, so that the 2 c.c. used in the test contained 1 mg. of sugar. When this is subtracted from the sugar obtained, we have just the amount of sugar in the blood. Originally 0.5 c.c. of blood was used, but only half the total (5 c.c. filtrate) is used in the test, so that the amount of sugar represents that in 0.25 c.c. of blood. From this it is easy to determine the amount in 100 c.c. of blood, by multiplying by 400.

"It is well here to call attention to the fact that for the titration to be successful the filtrate, after the addition of the dialyzed iron and centrifugalization, must be water clear. Two factors occasionally enter to prevent this. At times not enough Rochelle salts is added and at other times there is insufficient iron. To obviate the latter possibility we have been in the habit of using 5 to 6 c.c. of the iron solution. Students of the original Kowarsky article will note that he advises the use of 'Merck's liquor ferri dialysati oxidati diluted with an equal amount of water.' However, the liquor put out in this country is a 5 per cent solution, and must be used in its whole strength. Dilution according to Kowarsky's technic will spoil the test. At times the iron solution does not seem to maintain a constant strength, and often in the case of a new bottle it will be found necessary to use a little more or a little less than 5 c.c.—always being careful, however, that the total equals 10 c.c."

—*R. S. M.*

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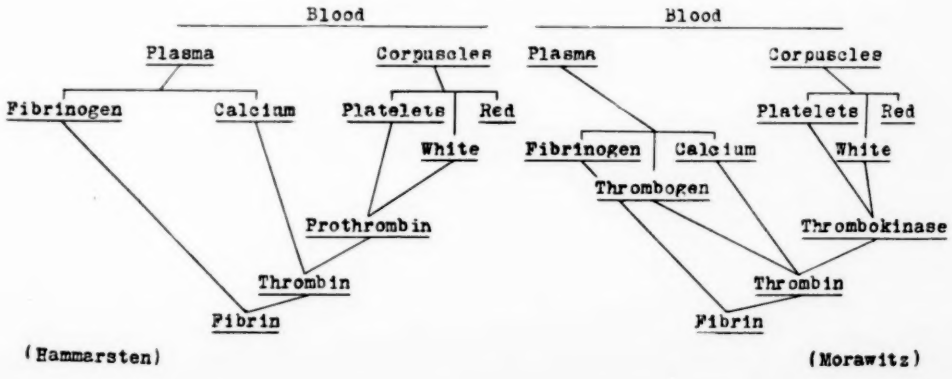
The Coagulation of the Blood

THE scientific investigation of the process of blood coagulation dates from the work of Hewson in the latter part of the eighteenth century. From his time down to the present many contributions have been made to the study, but the exact stages and factors concerned in the process are still matters of controversy.

Hewson found that the formed elements of the blood take no part in the formation of the clot. Buchanan showed that coagulation is a change of soluble fibrinogen into insoluble fibrin by the action of a second substance. Schmidt concluded that the process is the action of fibrin ferment (thrombin) on fibrinogen, the ferment being activated from prothrombin to thrombin by the action of a zymoplastic substance from disintegrating cells. Wooldridge laid stress on the importance of disintegration products of blood platelets, but he did not regard coagulation as a ferment action. Green, Arthus and Pages discovered the necessity of calcium salts, while Pekelharing and Hammarsten showed that the action of lime salts is on prothrombin and not on fibrinogen.

These studies have led to a theory which is generally accepted at present: Fibrinogen, a soluble proteid of the plasma is converted into insoluble fibrin by the action of thrombin; this is produced after the blood is shed by some precursor from the disintegration of leucocytes or blood platelets. Calcium salts are essential to the process. This is the basic theory at present, but recent workers disagree concerning both the formation of thrombin and the character of its action. Some maintain that prothrombin is changed to thrombin by the action of calcium salts. Among these are Hammersten, Pekelharing, and Rittger who concluded that prothrombin is produced by the disintegration of leucocytes and blood platelets. Howell believes that the prothrombin is present as such, but antithrombin inhibits the action of the calcium salts on it. A more elaborate theory of the formation of thrombin has been worked out by Morawitz, who found that thrombin is produced by the action of thrombokinase (from the disintegration of blood platelets and tissues) on thrombogen (a substance in solution in plasma) in the presence of calcium salts. The difference in the two theories can be made clearer diagrammatically.



The ferment or non-ferment character of thrombin is another point of dispute. Morawitz and his followers regard thrombin as a true ferment because it is not used up in converting fibrinogen to fibrin. Nolf and Rittger, however, state that the action of thrombin is not that of a ferment. According to Nolf, clotting is due to the interaction and precipitation of colloids. Rittger says fibrin is a simple union of fibrinogen and thrombin, and kinases act as particles of foreign matter in hastening coagulation.

The process of blood coagulation is still obscure but the research in this field has resulted in much information that has been given practical application in arresting hemorrhage, both in normal persons and in hemophiliacs. Numerous remedies for hemorrhage have been made use of, all of which have been found beneficial in some cases, and totally inadequate in others. Tannic acid, digitalis, ergot, epinephrin and gelatine have been commonly employed. Gelatine is used locally, but the process of heating it for sterilization deprives it of much of its action. It is more effective given by mouth when it is possible for treatment to extend over several months. There is one case on record where the blood of a hemophiliac coagulated so readily after eighteen months' treatment[1] that no blood test could be made. Rontgeno-therapy has been successful at times, but it has frequently been misused. Intravenous injection of sugar solution[2] is another method which has brought results, its benefit depending on a modification of osmosis. It has the advantage over salt solution because it is nutritive, and over blood serum because there is no danger of anaphylaxis.

It was early observed that injured tissue cells liberate a substance which accelerates coagulation, but whether this is of the nature of thrombokinase or of a thromboplastin which neutralizes antithrombin, is still undetermined. It is stated that the combined action of tissue and blood coagulins produces a greater effect on coagulation than the sum of their separate actions. Hemophiliacs often present a lack of thrombokinase in the blood but it does not always follow that there is a corresponding lack in the tissues. Hence tissue juices from the patient himself are available. These are used in connection with actual cautery where the benefit is ascribed to the necrosis of tissues, and also in the act of crushing and manipulating tissues around bleeding points.[3] Tissue extracts, especially of goiter, lymph glands, liver and others rich in coagulin, are employed locally. Experiments on animals[4] prove that the intravenous use of these extracts shortens the coagulation time materially, but this method applied to humans has proved disappointing so far. The danger in the intravenous use of these extracts was pointed out by Wooldridge who found that there is a distinct negative phase following injection, its extent and duration depending on the dosage and the condition of the animal. The negative and positive phases are analogous to those following the injection of toxins except that in the case of tissue extracts the phases are brought about within a few seconds. The intravenous injection of peptone solution affords another instance of two opposite phases. Immediately after injection, coagulation is hastened. If death does not result from intravascular clotting there follows a phase in which coagulation is retarded. The increase is thought to be due to the production of a great quantity of fibrin ferment and the decrease may possibly be due to the secretion

by the liver of an excess of anticoagulin. Peptone solution has been tried as a hemostatic, but its use, at least in one instance, was followed by intolerance and death.[5]

In general, the means which has brought the best results is that of supplying blood or one of its constituents. Dried fibrin, human or sheep, has stopped hemorrhage, when applied directly. Calcium is indicated when the calcium content is low as, for instance, in some forms of jaundice. This is supplied most commonly in the form of calcium lactate which is effective given by mouth when the treatment lasts several days.[6] A prompt though temporary effect is obtained by intravenous injections. The great success that has attended the employment of blood is perhaps due to the fact that besides providing new factors of coagulation it furnishes also nutrition and new immune bodies. Blood is used in large quantitiets in the fresh form, defibrinated and as serum. Defibrinated blood has been used both subcutaneously and intravenously, the latter method being the most active. The sera commonly employed are horse serum,[7, 8] even in the form of diphtheria antitoxin[9] when the normal serum is not available, and human serum.[10, 11, 12] The disadvantage of animal serum is the danger of anaphylaxis and of contamination and loss of strength if it has been preserved for any length of time. Fresh blood is efficacious if applied directly to the bleeding surface.[13] More frequently it is transfused from another individual to the patient.[14] This treatment has been used to a great extent recently for hemorrhage in the new born. The blood is injected into the sagittal sinus through the anterior fontanel. In indirect transfusion, the blood is received into an oiled vessel or is mixed with hirudin,[15] and it is then injected into the patient. These procedures retard coagulation. The oiled vessel presents a surface similar to that of the vessel lining and the hirudin acts as an antithrombin. Such a minute quantity is needed that it has no derogatory effects. In direct transfusion blood is passed directly from the vein of the donor to that of the recipient. Formerly transfusion of normal blood of a close relative was advocated, but it is becoming the custom to use entirely foreign blood as this has often been beneficial when the former proved of no avail.[16] It seems that the danger from dred transfusions there were only fifteen instances of macroscopic hemolysis, hemolysis has been exaggerated. One set of statistics[17] shows that in eight hunand in eleven of these cases there was recovery. It is considered advisable to make the test except in instances when the loss of time occasioned would prove dangerous.

These comprise the usual methods for the arrest of hemorrhage. Since the problem of coagulation is still unsolved, it is to be expected that seemingly contrary results will be obtained and will not be wholly accounted for. However, much of the confusion may be attributed to lack of discretion in the choice of treatment. More effort should be made to determine just what factor of coagulation is missing, or if all are present whether there is an excess of antithrombin. For instance, no amount of calcium will help a case where the difficulty lies in lack of prothrombin or fibrinogen, and tissue extracts are not indicated unless the bleeding is due to lack of thrombokinase or excess of antithrombin. One of the reasons why the use of blood has met with such extensive success is that the missing element whatever it is, is supplied from the normal blood.

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EDITORIALS

Experimental Arthritis in Rabbits

AN extremely interesting study on experimental arthritis in rabbits, published by H. K. Faber in the *Journal of Experimental Medicine*,[1] introduces a novel, and at the same time theoretically sound, point of view into the investigation of rheumatic disease. Past inquiries into the etiology of rheumatism have largely confined themselves to attempts to isolate bacteria from joints or to produce experimental infection in animals by injections of pure cultures systemically, or into the joints themselves, and it is, of course, familiar to physicians that many microorganisms have been held responsible for this protean disease. Loeffler[2] produced arthritis with streptococci as early as 1884. The work of Poynton and Paine[3] with the Gram-negative coccus they held responsible for rheumatism has been too recently under discussion to need comment. Rosenow's work on isolation of streptococci has called particular attention to the problem of bacterial origin of the disease, during the past two years. Achalme[4-8] believed the etiological factor to be a bacillus belonging to the aerogenes capsulatus group. Many bacteriologists have hesitated to assume that acute articular rheumatism was a disease of uniform bacteriological etiology largely for the reason that few experimenters have failed at one time or another to observe joint lesions in systemically infected animals when various different microorganisms were the infecting agents. It has seemed, however, that the relation

of the streptococci to the disease might be a more intimate one than that of any of the other bacteria.

The line of research followed out by Faber was suggested, he states, by the work of Herry[9] in 1913, who injected into the joints extracts of streptococci, isolated from the blood in cases of rheumatic fever, and fifteen days later followed this with an injection of the living bacteria. Faber calls attention to the interesting fact that in many of the cases of experimental arthritis produced in animals there has been a definite incubation period before the joint lesion occurred, and that Cole,[10] Shaw,[11] and later Schloss and Foster,[12] found that arthritis in animals was obtained only after repeated injections. It seemed obvious from this that sensitization of the joints to the microorganisms might be a factor in the selective localization of the infection. In his first experiments Faber used streptococcus viridans strains. The animals used were rabbits ranging from 1,200 to 1,800 grams. When the bacteria were injected intravenously it was found that no arthritis developed after one and two injections, but that at least two preliminary sensitizing doses were needed before any of the rabbits developed arthritis.

In another series of experiments he attempted to sensitize the joints locally. Suspensions of the organisms were injected into the left knee, using care not to infect the periarticular tissues. The result was usually an arthritis which after two to four weeks got well, the joint contents becoming normal. In most cases he used dead bacteria for such sensitization. At varying periods after the joints had become normal, intravenous injections of the same organisms were given. In almost all of fifteen rabbits gross signs of arthritis developed. This seemed to show that sensitization of a joint was possible and that anthritis might develop as a result of repeated inflammation of a joint once sensitized when the same bacterial cause was applied. However, it was still an open question whether or not such sensitization was specific. Crossing with streptococcus and pneumococcus resulted in failure of reaction. However, when closely related strains of streptococci were used for sensitization and subsequent injection, slight reactions (doubtful) were obtained.

The work is extremely interesting in showing that actual sensitization of a joint may bring about a specific reaction that predisposes to subsequent joint inflammations when the homologous organism reinfects the body. It would also suggest that a number of different bacteria can cause arthritis, and that, as Faber correctly suggests, one organism is not always at fault. That the streptococcus, and chiefly that of the viridans group, should be the one most commonly causing the disease in human beings is rather natural owing to the relations of virulence and resistance, the method of invasion of this organism, and its common occurrence in and upon the human body. However, Faber's work opens the possibility that the occurrence of rheumatism, or rheumatic joint infections, depends not only upon the presence of a microorganism capable of invading the joints, but of a previous specific hypersusceptibility of the joint tissues for this organism caused by a preceding inflammation.

Incidentally the work of Herry and of Faber opens up a line of reasoning more broad than its strict application to the explanation of rheumatism. If his views regarding rheumatism should turn out to be correct, there is no reason

why similar sensitization of other tissues of the body may not explain in general the selection of various parts of the body for specific injury when other parts equally exposed to invasion by the microorganisms are spared.

—*H. Z.*

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Origin and Spread of the Cardiac Impulse in the Auricle

WITH the discovery that it is by the so-called bundle of His and Kent, or the auriculo-ventricular bundle, that the cardiac impulse passes from the auricle to the ventricle, interest soon became aroused as to the exact place in the auricle at which the impulse originates. It had for long been known that, in the cold-blooded heart, the impulse definitely starts at the sinus venosus and spreads over the auricles to the ventricles, and it had also been observed, in the mammalian heart, that the bases of the large veins, where these join the auricles, are likely to continue beating for a considerable time after the rest of the heart has ceased to beat.

The first definite progress in the localization of the site of origin of the beat in the mammalian heart was furnished by the discovery of Keith and Flack of a peculiar type of tissue located at the junction of the superior vena cava and the right auricle. In this position they found a small artery which is surrounded by fibrous tissue containing numerous peculiar muscle fibers, some nerve cells and some nerve fibers. The muscle fibers were found to have a structure not unlike those of the auriculo-ventricular node. These anatomists suggested that it might be in this "sinus node" that the cardiac impulse originated.

To put the hypothesis to the test various methods have been employed. These include: (1) injury of the node in various ways; (2) determination of the comparative rhythmicity of strips of the auricular walls, which contained or did not contain nodal tissue; (3) determination, by the use of galvanometric curves, of the relation of the node to the seat of origin of the cardiac impulse. The conclusions which have been drawn from these investigations have not been entirely in harmony. Lewis, Zahn, Meek and Eyster, etc., have held that the node is the site of origination of the beat, whereas Erlanger maintains that the structure has no initiative not shared by other auricular tissue in the region surrounding it.

Closely linked to the question of its site of origin is that of the course of the excitation wave in the auricles. Does it travel by some specially provided path running between the sino-auricular and auriculo-ventricular nodes, or does it spread uniformly over the whole auricle. If the former should be the mode

of propagation, the impulse will reach the auriculo-ventricular node before the auricles go into contraction. The importance of knowing exactly whether this is the case is evident in connection with the whole question of cardiac arrythmias.

We shall not attempt to review all of the literature pertaining to this question which has recently appeared, but will confine ourselves to the papers of Eyster and Meek[2, 3] and of Lewis and his pupils.[4, 5] But to follow the work of these investigators, it is essential that we understand clearly the principles of the methods which they have employed. These principles are very clearly and simply set forth in the recent Harvey lecture by Lewis. Briefly summarized the main points are these: When a galvanometer is connected by means of unpolarizable electrodes with two parts of a denervated muscle, a current will be found to become established when a wave of contraction passes over the muscle from one end to the other. The portion of muscle that contracts first becomes electrically negative to the rest of the muscle. As the wave of contraction passes along the muscle, the negativity, as it is called, gets less at the end at which the wave started, until, when the wave is in the center of the strip, neither end of the muscle shows any difference in potential, so that the galvanometer will come to rest. As the wave reaches the farther end of the muscle, this in turn becomes negative, and the needle will swing in the opposite direction. It is evident, then, that the initiation of a muscular contraction wave occurs at the electrode which is negative first. Another important observation is that the movement of the galvanometer in the above experiment is most marked when the two electrodes are at the extreme ends of the muscle; that is to say, the amplitude of the negative wave is greatest when the time interval between the receipt of the excitation at the two contacts is greatest.

The application of these facts to the study of the initiation of the beat in the auricle requires that we should consider one other proposition, namely, this: If a pair of contacts be arranged in the center of a circular sheet of muscle, and the edge of this sheet be stimulated at different points, the amplitude of deflection on the galvanometer will be greatest when the contacts are radial to the points of stimulation, for under these conditions, it is evident that the greatest possible interval will exist between the arrival of the wave at the two contacts.

Before proceeding to consider the manner in which these principles may be applied in the location of the pacemaker of the heart, it is important to call attention to the methods which have been employed to ascertain exactly the positions at which the electrodes were placed on the auricle. In Eyster and Meek's work the point of application of the electrodes was marked by ligatures, and after the experiment was over, the heart was examined microscopically so as to locate exactly the position of the ligatures. Lewis was even more careful. Scale drawings were made of the auricle during the experiment, certain landmarks being employed so as to locate the exact position of the electrodes. After the experiment, the auricular portion of the heart was hardened, dehydrated and embedded *en masse* in paraffin. The impregnated auricle was then compared with the original scale drawing and a new drawing was made, upon which the chief muscular bands of the auricle were sketched in their relationship to points of application of the electrodes.

Regarding *the point of origin of the beat* the following facts indicate that

it is in the sino-auricular node. First, when the contour of the wave is compared in electrocardiograms taken with the two electrodes applied at different parts of the auricle, it is always found that the greatest amplitude of movement is obtained when the line joining the electrodes converges to the sino-auricular node. From experiments with the circular sheet of muscle above alluded to, it is evident that the stimulus to produce this condition must arise in the neighborhood of the node.

Second, if one electrode be placed on the sino-auricular node and another electrode moved about from place to place on the auricle, the electrode on the node is always negative to the other. This is not the case if the electrodes are on any other parts of the auricle.

Third, by comparing normal electrocardiograms from lead 2 (i. e., when the right fore limb and the left hind limb are connected with the galvanometer) with electrocardiograms taken when beats are started by applying artificial stimulation to the various parts of the auricle, it is found that the normal curve is obtained only when the stimulated part is in the neighborhood of the sino-auricular node. This is particularly noticeable in the case of the P-wave, which is the characteristic auricular wave, and is obtained, after artificial stimulation of the auricle, only when this stimulation is at the sino-auricular node. If the stimulation be at the appendix or at the superior vena cava, the P-wave is distorted although the other waves appear normal.

Fourth, by taking simultaneous electrocardiograms from a direct lead on the auricle and a standard limb lead (Lead 2, for example) and determining, by exact methods of mensuration, the time of onset of the excitation wave, relative to P in the standard, in various regions of the auricle, it is found that the first appearance of the excitation wave occurs earlier when one electrode is over the upper end of the sino-auricular node, and that, in other regions of the auricle, it always appears at a later interval.

Fifth, careful examination of electrocardiograms from different parts of the auricle shows that the main wave of negativity is sometimes preceded by slight positive waves, that is, waves that dip below the base line. It will further be noticed that the waves showing no initial deflection are always obtained when one electrode is on the sino-auricular node. Lewis and his pupils, who have investigated this point, have come to the conclusion that the deflection waves preceding the main wave of negativity are really due to extrinsic influences acting on the electrodes. In other words, the electrodes pick up electric discharges from distant areas of muscle, while these are in a condition of contraction. Thus, if electrocardiograms be taken from two leads on the auricular appendix, a very distinct initial deflection will precede the main wave of negativity. If now the base of the appendix be crushed so that no wave of contraction can reach the appendix, the wave of negativity will disappear (that is to say, the intrinsic deflection), but the initial or extrinsic deflection wave will remain, being conducted to the electrode from a distant part of the auricle. "All curves from leads at a distance from the sino-auricular node or outlying leads, as we may call them, therefore give curves of a more or less composite form; consisting of a main deflection, which corresponds to the arrival of the excitation process, and diminutive initial deflections which are due to the passage of other portions of the auricular muscle into the excitatory state." From these considerations it follows that the interval between the intrinsic and ex-

trinsic deflections should be longest in leads that are farthest from the node, and that they should approach as one of the contacts approximates the node, until over this structure, the extrinsic deflection is no longer recorded. Such has been found to be the case. The importance of these observations rests on the fact that previous observers have not sufficiently regarded the influence of extrinsic deflections in interpreting the curves.

Taking all these facts together, then, there remains not the shadow of a doubt that the beat of the heart originates in the upper club-shaped extremity of the sino-auricular node. So far as we are aware, the only authority who has disputed this conclusion is Erlanger, who has pointed out that a very feeble, undetectable negativity might originate somewhere near the node, but only become sufficiently pronounced to show itself when it affected the more reactive tissue of which the node is composed. Eyster and Meek have tried to remove this objection by showing that similar results to those recorded from the outside of the auricle are obtained when the electrodes are applied, not to the exterior wall of the auricle, but to its endocardiac surface.

It is important to note that Eyster and Meek[3] have conclusively demonstrated the unreliability of using observations from the dying mammalian heart for the purpose of determining the site of origin of beat. It is of course well known that the power of contraction remains in the venous and auricular regions for a considerable time after the ventricles have ceased to beat. This part—the *ultimum moriens*—in most hearts is situated somewhat lower than the sino-auricular node. Though this is the last part of the heart to cease contracting, that does not mean that it is the part of the heart in which the beat ordinarily originates. It simply means that it is the part of the auricle in which the power of contraction remains for the longest time after death.

The course of the excitation wave in the auricle and the rate of its conduction.—This can be determined by two methods, which we may call the direct and the indirect. In the direct method a series of pairs of contacts is placed on the auricle, each pair being in a radial direction to the sino-auricular node. The time at which the excitatory process arrives at that contact of each pair which is proximal to the sino-auricular node is then accurately determined from the galvanometric record. The exact distance between the contacts and the sino-auricular node is now measured and from the data the average transmission time is estimated.

In the indirect method the onset of the negative wave from different leads is compared against a standard. Considerable difficulty has been experienced in finding a suitable standard for this purpose. Eyster and Meek have used the mechanical systole of the auricle, that is to say, they compare the onset of negativity in any region with mechanical systole of the right auricle. The chief objection to this method is the great difficulty of knowing, from the mechanical record, the exact moment at which this act starts. Lewis and his pupils have also used an indirect method (Sanderson's) which, however, is too complicated for description here. It is admitted by Lewis, however, that this indirect method is applicable only when the contacts are strictly in line with the sino-auricular node, that is to say, on the taenia terminalis.

The results of the above investigators are not in entire harmony with regard, either to the relative rate of propagation of the wave to different portions of the auricle, or to the actual rate at which the wave travels. Lewis maintains

that the transmission rates are uniform from the node to all parts of the auricle, with the exception of the superior vena cava, in which the rate is considerably lower. One thousand millimeters per second represents very fairly the average rate at which the wave travels. Eyster and Meek, on the other hand, state that the wave is propagated throughout the sinus node and spreads to the contiguous venous region and to the auriculo-ventricular node with considerable rapidity—reaching the mouth of the superior vena cava in 0.01 second or less—whereas its passage to the auricle takes longer, namely, 0.02 second. There is, therefore, a delay in the passage of the wave to the auricle, which indicates that the excitation must spread to the auriculo-ventricular node before involving the right atrium. They conclude: "This leads to the inevitable conclusion that the cardiac impulse spreads to the ventricle and to the right auricle by different paths, and does not pass to the ventricle through the auricle, as ordinarily stated."

Lewis and his collaborators place great emphasis on the fact that the determining factor in the spread of the excitation wave is the disposition of the auricular muscle fiber. In their heart specimens, as above described, they could show clearly that the muscle fibers all radiate in a curious fan-shaped manner, from a point which lies immediately below the sino-auricular node, to all parts of the superficies of the right heart. They have named this the *concentration point.* At the end of the vena cava the muscle fibers are arranged more or less circularly, which may explain the delay in transmission which these authors found at this place. The results of their investigations may therefore be summed up by stating that the excitation wave in the auricle spreads in the same manner as a fluid poured upon a flat surface would spread. Its edge advances in an ever widening circle until the whole surface is covered, and the rate of spread is approximately 1000 millimeters per second.

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[2]Eyster and Meek: Experiments on the Origin and Propagation of the Impulse in the Heart—The Point of Primary Negativity in the Mammalian Heart and the Spread of Negativity to Other Regions. Heart, 1914, v, 119.
[3]Eyster and Meek: Experiments on the Origin and Propagation of the Impulse in the Heart—Observations on Dying Mammalian Hearts. Heart, 1914, v, 137.
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[5]Lewis: Lectures on the Heart, 1915 (P. Hoeber, New York).

—*J. J. R. M.*

Nervous Influences and Edema

THE conception that the nervous system plays a major role in such conditions as inflammation and edema, is a widely held one, chiefly perhaps because there has been, until very recent times, no other explanation which could be offered. And yet there seems to be modern evidence that the nervous system plays only a minor role in either process; that it plays no essential part in their production, but merely increases or decreases the rapidity of their courses. In the absence of nervous impulses, either process will follow its normal course although that may be lengthened.[1]

In a recent article Heitz and DeJong[2] discuss the relation between nervous

influences and edema. They commence by saying that Vulpian showed that section of nerves is accompanied by vaso dilatation which facilitates serous transudation and infiltration of the tissues. They mention the experiments of Claude Bernard, Ranvier and others which perhaps form the basis of the neurogenic conception of edema. They call attention to clinical experiences, in the neuritides, infections, myelitides, encephalitides, and other types of cerebral lesions in which edema occurs, which seem to substantiate the neural conception. They have collected many facts which as they say lead to the conclusion that edema is only a manifestation of the accumulation in the tissues of retained chlorides. They say that the facts lead to the conclusion that edema is a manifestation of the accumulation in the tissues of chlorides which are not eliminated by the kidneys and that vaso-dilatation has only the effect of influencing their distribution in the tissues. But this is not the interesting fact that merits most attention, for whether chloride retention is the cause of edema or not, is a matter of much discussion with, we think, the best evidence in the negative.[3] The essential fact that is brought out by Heitz and DeJong is that the nervous system is not an important mechanism in edema. A nervous system lesion, they say, is powerless to cause edema. And when edema arises in the course of a disease of the nervous system, it calls attention to the presence of a coincident renal or cardiac abnormality which up to the time of observation had remained unnoticed.

These conclusions rest upon the observations of cases, which are quoted, of cerebral lesions accompanied by hemi-edemas, and the authors state, it is just such cases which have formed the main basis of the neural doctrine of edema.

Just why the edema should affect the paralyzed limbs is not stated. It might be suggested that the cause of this is the decreased circulatory activity in the affected tissues, which prevents normal oxidative processes and which also shows the rate of removal of waste materials.

[1]Woolley: Jour. Amer. Med. Assn., 1914 (63) 2279; also Centr. f. allg. Path., 1915 (26) 218.
[2]Heitz and DeJong: Arch. d. Mal. du Coeur, 1915 (8) 148.
[3]For the arguments see Fischer: Oedema and Nephritis, New York, 1915 p. 525, 529, etc.

—*P. G. W.*

Ethylhydrocuprein and Pneumococci

HENRY F. MOORE, working at the Rockefeller Institute for Medical Research,[1] has again studied the bactericidal effect of ethylhydrocuprein on pneumococci. This substance was first introduced by Morgenroth[2] who found that it had a more or less specific antagonistic action for pneumococci. The same results were achieved by A. E. Wright[3] and others, and Moore's observations further confirm them. Moore used rabbits as his test animals. He gave these animals subcutaneous injections of ethylhydrocuprein, dissolved in distilled water or sterile olive oil, finding that a dose of 0.1 gram per kilo of body weight was well tolerated. It appears from his protocols that doses exceeding this amount usually were toxic. An animal receiving 0.2 grams per kilo showed severe toxic symptoms, as did one receiving 0.15. Animals receiving 0.125 in several cases showed "a tendency to lie quiet for some hours after the injection." When the base of the drug, dissolved in oil, was given intramuscularly it was more toxic than

when given subcutaneously, and the bactericidal effect on the pneumococci noted in the serum was neither so prolonged nor intense as when the drug was subcutaneously administered. The tolerance for the drug was greatest when the hydrochloride, dissolved in distilled water, was put into the stomach, but there were practically no bactericidal effects noted in the serum in these cases.

The serum of animals treated with ethylhydrocuprein subcutaneously, exerted a distinct bactericidal action on pneumococci. The effects were greatest, as stated before, when the base (optochin base) was given subcutaneously in oil. The intravenous route was found to be very toxic, and even in such cases the effects were not prolonged. Bactericidal action of the serum was at its highest point about an hour after the drug had been given. When given to man by mouth in doses of 0.5 grams (of the ethylhydrocuprein hydrochloride), no toxic symptoms occurred. The same dose given in sterile distilled water subcutaneously had no serious effects, though slight pain in the legs, a slight rise of temperature, and a little hyperemia at the site of injection occurred in one case; in the other case there was a slight headache, with similar infiltration around the area of injection, which disappeared within a few days. The serum of individuals to whom such a single dose of the drug had been given had a definite inhibitory effect on pneumococcus growth which lasted for a number of hours, the bactericidal action being much more feeble than in the case of the rabbits.

Moore, very wisely, draws no conclusions concerning the therapeutic possibilities of the drug in pneumococcus infections, but states the facts as he found them. It would seem that his experiments definitely confirm the claim that this substance lends a decided bactericidal power for pneumococci to the serum of animals and of man receiving it, but the small margin between effective amount and toxic dose and the short duration of the bactericidal effects would seem to indicate that in the present form no great therapeutic developments can be hoped for.

[1]Jour. of Exper. Med., Nov. 1, 1915, xxii, p. 551.
[2]Berl. klin. Wchnschr., 1911, xlviii, 1560, 1979.
[3]Lancet, 1912, ii, p. 1633, 1701.

—*H. Z.*

Intestinal Stasis

INTESTINAL stasis is fundamentally a mechanical problem, no matter what its sequelæ may be, and it is the mechanical problem that one must solve if one is to understand the underlying causes. A healthy, normal bowel will not permit of stasis, but will carry on its motor functions with ease and regularity. When one says normal bowel, one postulates normal conditions of living.

But, it happens, stasis of greater or less degree occurs in individuals who are living an apparently normal existence. No longer is the regularity of the gut maintained; no longer is its function carried on automatically. To account for these abnormal states it is said that the musculature of the bowel has lost its tonicity, which means that it is not able to contract as powerfully, or that it does not contract rhythmically as it should. It is said that kinks occur (congenital or acquired) and that these, usually due to bands or adhesions, pre-

vent the even progress of the intestinal contents to their normal destination. As a result of such a condition, the intestine becomes dilated, the muscle fatigues so that it no longer is able to do its duty, and then absorption of bacteria or toxic substances takes place with subsequent damage to health. When such anatomic distortions are severe, they interfere with the functions of the bowel, no doubt, but when they are less severe, and this is the rule, they do not interfere to any great extent with the motor functions, and since in very many cases there is no external or visible reason for the stasis, something intrinsic must have gone wrong. To say that the muscle is atonic means nothing.

Recently Keith[1] has given, in the Cavendish Lecture, a possible, and plausible explanation of stasis which reaches deeper into the subject than any other one. It will be remembered that Keith has studied intensively the "nodal" and "bundle" tissues of the heart, and that upon his researches with those of other writers our working knowledge of the controlling muscular mechanism of the heart is based. Keith has interested himself more recently in that part of the gastro-intestinal tract which he believes is analogous to the cardiac controlling system. This is the myenteric (Auerbach's) plexus. This plexus Keith has studied in a large series of human specimens as well as others taken from various other mammals, and his studies have convinced him that it is not a simple structure composed merely of nerve fibres and nerve cells. These it contains, but besides these, are branching intermediate cells which appear to become continuous with processes of certain groups of muscle cells on the one hand, and with the branched processes of ganglionic cells contained in the nerve fibres of the plexus, on the other.

Upon the basis of these observations, Keith conceived the idea that the myenteric plexus is analogous to the nodal and conducting system of the heart; —that as in the heart the efferent nerves which influence the contractive tone and rhythm of the bowel end, not in the muscle, but in the myenteric plexus, which in its turn effects the contractions of the musculature of the gut.

In the course of his researches Keith found that there are certain points in the course of the gastro-intestinal tract where the conducting system is collected into rather larger masses than is the general rule. The points correspond to the nodes of the heart. Such nodes were found at the gastro-esophageal junction, where gastric contractions are initiated; in the ileo-caecal region; and in the rectum. There appears also to be an initiatory point in the duodenum proximal to the entrance of the common bile duct. From each of these areas the fibres of the myenteric plexus seem to extend distally. Between each of these areas the rhythm gradually decreases.

In applying these observations to intestinal stasis Keith says that "in passing along the alimentary tract, food is propelled through a series of zones or segments, each furnished with its own pacemaker and its own rhythmic contractions. In the heart we find two such zones—an auricular and a ventricular; in the normal heart the sino-auricular node is the master pacemaker. But a block or imperfection in conduction may occur between the two zones of the heart, with the result that 'back pressure'—a venous stasis is produced." He supposes that irregularities may occur in the same way in the nodal and conducting mechanism of the alimentary canal, and when they do, he finds that they occur where they should be expected—at points where one rhythmical zone passes into the succeeding one. Blocks are found at the gastro-esophageal

junction, at the second part of the duodenum, at the duodeno-jejunal junction, at the ileo-colic. Not only must these nodes be healthy but they and their rhythmic zones must be closely co-ordinated. Disturbance in any one segment upsets the rhythm in all segments. Distention of the duodenum inhibits the action of the ileum; duodenal disturbances upset the rhythm of the stomach; disease of the myenteric tissue of the caecum will produce abnormalities in the movements of the lower ileum.

Finally Keith says that radiograms have failed to produce evidence of obstruction situated at bands or kinks; there is no hypertrophy of the muscular coats above the bands or kinks; and where acute flexures are produced experimentally, stasis does not result. On the other hand, there is good evidence which points to a gross derangement in the action of the musculature of the whole colon in stasis of the great bowel.

In this material of Keith we have for the first time a truly physiologico-anatomic reason for stasis, but a reason which must be studied and confirmed. If there is such a conducting and co-ordinating neuro-muscular (myenteric) mechanism, how is it deranged? In the heart we find that a block may arise because of a lesion of one of the nodes, or of the branches of the bundle itself, or of the myocardium alone. These lesions may be the result of inflammations or degenerations. Edemas of the tissues or cellular infiltrations of the tissues about the bundle may act by compressing it; drugs carried to the bundle by the blood may modify it; and influences acting by way of the vago-sympathetic system may increase or decrease its powers of conduction. It is perfectly possible that in acute intestinal infections the myenteric plexus is temporarily damaged, and that in chronic inflammatory processes it is permanently affected so that the normal rhythm is interfered with so that perhaps, as in the heart, only every other impulse to contraction is effective. And so one might proceed in drawing the analogy. Keith's is a very suggestive work.

[1]Keith: Lancet, 1915 (2) 371. See also Brit. J. Surg., 1915 (2) 576.

—*P. G. W.*

Death by Hanging

IN hanging death is generally assumed to be due to asphyxia, although in a small per cent of the cases of official execution by this method the neck may be broken, and in some rare instances still greater injury to the tissues, both the soft and the bony parts, may be done. Indeed, there are recorded cases in which the head has been completely severed by hanging, the interval between the drop and death is quite variable, depending upon the completeness with which the windpipe is closed and the distance of the drop. In old people there may be some ossification of the trachea, and this quite naturally would interfere with the action of the ligature, and death would be slow in proportion to the extent of the hardening of the tissue. Displacement of the second cervical vertebra occurs rarely, but has been observed when corpulent persons are executed, or when a long drop is given. The location of the noose has something to do with the speediness with which death results. When the cord is placed below the cricoid cartilage asphyxiation follows more speedily than when pressure is made upon the larynx, because with the ligature in the former location

the air is more completely shut off. With the ligature properly placed and with a drop of six or more feet, death by hanging appears to be practically instantaneous, and free from physical suffering. It is true that in practically all cases of legal execution by hanging there are violent movements or convulsions of the trunk and extremities after the body drops, but these are probably unconscious and unaccompanied by pain. When compression of the windpipe is complete and the weight of the entire body is placed on the cord, death certainly occurs within two or three minutes, and after this time resuscitation is impossible. In many cases of attempted suicide by hanging, resuscitation may be brought about after a much longer period, but in these instances the loop has not been adjusted with skill, and in the great majority of them the body is partially supported in some way.

Descriptions of the external appearances after death by hanging have for the most part been taken from observations made at legal executions, and in these cases the face is livid, frequently distorted, sometimes swollen. The eyes are glaring, red, and sometimes markedly protruding from their cavities. The tongue is swollen and either protruding or clenched between the teeth. A frothy mucus, stained with blood, drops from the mouth, the line of the cord around the neck is marked, showing in many instances laceration of tissue, and in others numerous ecchymoses. The hands are clenched, and the lower limbs usually flexed. While these appearances are quite marked and constant in cases of legal execution by hanging, they are usually much less distinct when suicide has been attempted by this method. In suicidal cases the face is frequently pale. There may be no protrusion of the eyes. The line of the cord varies greatly, and in proportion to the weight placed upon it. If the body be partially supported the cord may leave but slight evidence of its location. The nature and width of the cord markedly influence the extent to which violence to the tissue is done. If a suicide hangs himself with a towel, there may be in fact no noticeable mark about the neck. While the hands are usually clenched in legal execution by hanging, this is by no means universally the case in suicides.

On postmortem examination after death by hanging there is found in all the abdominal and thoracic organs and in the brain, as well, marked venous congestion, and as is true in other forms of death from asphyxiation, the right side of the heart is more commonly distended and more completely filled than the left side, and the blood in the heart is frequently fluid, although this is not constantly the case. Venous congestion is often marked, and cerebral hemorrhages are by no means uncommon, but are more frequently found after violent hanging than in suicides.

The expert may be asked to determine whether or not death was induced by hanging. In answering this question he must rely very largely upon evidence furnished by the pressure of the cord. It has been shown experimentally by Devergie that if a corpse immediately after death be suspended by a cord around the neck, redness and even ecchymoses along the line may be induced, and Vrolik showed that when a body was thus suspended one hour after death a distinct livid line, corresponding with the course of the cord, might remain. It follows from this that so far as the mark of the cord is concerned there may be cases in which the expert can only say that the cord was applied during life or immediately after death. Of course, where great injury has been done, and

blood has flowed from penetration of the tissue there can be no hesitancy in deciding that death was caused by hanging, but the fact remains that there may be instances where the evidence furnished by the line of coloration caused by the cord leaves one in doubt. It has been claimed by some that the mark of the cord serves not only in deciding the point whether or not death was due to hanging, but the more difficult question as to whether the case was one of suicide or one of murder. It has been claimed that when the mark of the cord is circular and runs along the lower part of the neck the case could be only one of murder. However, there have been several cases of undoubted suicide in which the mark made by the cord was situated in exactly the place and had the form which it had been claimed could not occur in suicide. In one or two celebrated cases, notably that of the death of the Prince de Condé, in 1830, it was argued that the position of the dead body indicated homicide, and in fact was such that the case could not be one of suicide. This claim was evidently founded upon error. It was argued that death from hanging could not occur when any part of the body rested upon a support. The body of the Prince was found to be partly supported, and it was claimed that he did not die from hanging, but that he was murdered, and his murderer had partially suspended the body in order to make it appear that he had committed suicide. A person may hang himself and still stand on the floor, sit in a chair, or partially lie in bed. It is only necessary to put the proper noose around his neck and to throw the weight of a portion of his body on the cord, in order to commit suicide by hanging. A man may stand on the floor, put a noose about his neck, attach it to some object above him, and then take his feet from the floor, flexing his legs, and hold himself in this position until he becomes unconscious and unable to stand, and when his feet drop to the floor the weight of his unconscious body is sufficient to complete the death which he has consciously undertaken. Then, if the body remains in this position until rigor mortis comes on, it may appear that the man stands with a loose noose about his neck, and without any tension on the cord. The following interesting case is reported by Taylor: "In 1832 a man was found hanging in his room with his knees bent forwards and his feet resting upon the floor. He had evidently been dead for some time, since ca-daveric rigidity had already commenced. The manner in which this perso[illegible] working mechanic) had committed suicide was as follows: He had made a slip knot with one end of his apron, and having placed his neck in this he threw the other end of the apron over the top of the door, and shutting the door behind him, he succeeded in wedging it firmly. At the same moment he had probably raised himself on tip-toe and then allowed himself to fall. In this position he died. The weight of his body had already sufficed to drag down a part of his apron, for it seemed as if it had been much stretched. The deceased was in the position in which the body of the Prince de Condé was found, and the depression produced by the ligature on the neck was, as in that case, nowhere ecchymosed."

When the expert is called upon to examine a person supposed to have met his death by hanging, he should carefully examine every part of the body for evidence of external violence. If bruises, wounds or other evidence of injury be found, the surrounding objects should be examined with reference to their nature and position in order to determine whether or not the injuries found

might have been inflicted by them accidentally in committing suicide, or whether they point to homicide. In committing suicide by hanging the individual may place himself upon a chair, table, or some other elevation, adjust the cord, and fall in such a way as to bruise or lacerate his flesh, or even fracture a limb. All these possibilities should be taken into consideration in deciding whether or not death was due to hanging.

A closer study of the manner of death in hanging may be profitable. While closure of the trachea and death by mechanical asphyxiation are the objects sought and usually attained, there are certain complicating and modifying factors. When the noose is placed about the neck and the weight of the body, either wholly or in large part, put on the cord, death sooner or later results, and may be due to one of three causes acting individually or collectively. The noose incloses respiratory, circulatory and nervous connections and death may result from the interruption of the function of one or all of these. Undoubtedly in the great majority of hangings all of these connections suffer more or less and injury to each contributes to the final result. When the respiration is completely interrupted death within three minutes is certain, but in many instances of even legal hanging the passage of air is not wholly prevented. Complete arrest of the flow of blood through the carotids leads to immediate loss of consciousness, but when this is the only or chief injury done, resuscitation after relatively a long time is possible. Compression of the pneumogastric nerve may lead to immediate arrest of respiration, even in case the passage of air through the trachea is not mechanically interfered with; then, in legal execution by hanging, when the body is dropped some distance, the spinal cord is more or less injured, a vertebra may be fractured and indeed the head may be severed from the trunk.

That death may be caused by hanging without asphyxia has been demonstrated by men hanging themselves successfully while wearing tracheotomy tubes and with the cord placed above the incision in the trachea. Reineboth[1] has collected the earlier literature bearing on this subject, has reported a case and recorded his own experiments on animals. A man, who was wearing a tracheotomy tube on account of a tumor involving the trachea and esophagus, placed a cord above the tube and successfully hanged himself although he could touch the ground with his feet. Reineboth's animal experiments confirmed the earlier researches of Misuraca and established the fact that tracheotomy does not save animals from death by hanging but that the tracheotomized animal lives longer after suspension and that the appearance both *in vivo* and postmortem are not the same. The longest time that a normal rabbit lived after suspension was 3.3 minutes, while the longest time that a tracheotomized animal lived was 19.15 minutes. Bertelsmann[2] reports a case quite similar to the preceding. A woman who was wearing a tracheotomy tube was found dead fifteen minutes after she had been seen. Her knees touched the floor and her hands were folded across her bosom, so that she might easily have saved herself. She probably became immediately unconscious from the compression of the blood vessels.

Hofmann[3] seems to have been the first to call attention to the influence of arterial compression in hanging on the sudden loss of consciousness. He stated that the sudden loss of consciousness and the more speedy death, compared with that due wholly to asphyxia, occurring in hanging, are caused by compression

of the blood vessels and injury to the vagus nerve. This statement was seriously questioned until apparently settled by the thorough researches of Haberda and Reimer[4] whose conclusions are stated as follows.

1. The occlusion of both carotids in hanging, as claimed by Hofmann, cannot be denied.

2. In typical hanging both vertebral arteries are occluded. This interruption of the blood flow accounts for the sudden loss of consciousness.

3. There may also be suspension of the heart beat in diastole. Whether this is caused directly by injury to the vagus or reflexly through the laryngeal is left an open question.

4. This nervous effect, in cases of incomplete interruption of the blood flow, may hasten unconsciousness and delay asphyxia.

5. Brain pressure has no marked influence on the phenomena of death by hanging.

6. Traumatic injury to the laryngeal nerve probably has some effect in arresting respiratory movements, as suggested by Ignatowsky.

The third important factor in determining the phenomena of death from hanging is found in the injury done the vagus and its branches, especially the superior laryngeal, and its branches. Many years ago Czermak[5] called attention to the fact that pressure on the vagus may markedly increase the length of the interval between heart beats. This finding has been repeatedly confirmed and if such an effect can be induced by pressure on the vagus with the finger, it is easy to believe that serious results may follow the greater and more violent pressure of a hangman's noose. The experimental evidence on injury to the trunk of the vagus in hanging has been somewhat contradictory. However, the studies of Placzek[6] seem to show that the constriction of the noose has but little if any effect upon the vagus itself, because this nerve is protected by adjacent and superimposed muscles and that the effect of a noose is quite different from that of a finger nail that may be pressed forcibly upon one point. That the superior laryngeal is often injured and that this may and does contribute to the causation of death from hanging seems quite well established.

Usually in hanging the noose is placed above the thyroid and between this and the hyoid bone. With the cord in this location the base of the tongue is pressed against the posterior wall of the pharynx, the posterior nares are closed by the soft palate, and the apex of the larynx is brought upward and backward. In this way the passage of air may be wholly prevented. With the cord across the thyroid the occlusion of the windpipe may be only partial.

Haughton of Dublin, many years ago, investigated the mechanism of hanging and concluded that the most speedy and painless death is secured by placing the knot under the chin and allowing a fall of from ten to fourteen feet, inasmuch as by this method the spinal cord is fractured. Louis, after observing this method of legal execution, concluded that the executioner should give the body a violent twist as it falls, claiming that this movement fractures the odontoid process, dislocates the upper cervical vertebræ and results in instantaneous death.

Loss of consciousness in hanging occurs as soon as the noose is tightened by the weight of the body and the whole weight of the body is not required. The instantaneous loss of consciousness is shown by the fact that the suicide

never attempts to save himself after tightening the cord, although in many instances he might do so by straightening his legs or extending his arms. The same thing has been repeatedly demonstrated in accidental hanging. There are several cases on record where children in play have hung one another and if the victim throws a part or the whole of his weight against the cord he makes no attempt to save himself. Still more striking are some instances in which men in studying the sensations of asphyxia have carried the experiment beyond control. There are other instances in which there are strong reasons for believing that the suicide was seeking sympathy and not death. He provides himself with objects that he can easily reach with the intention of being found half dead, but when the cord tightens he loses consciousness and is no longer able to save himself from his folly. Hanging oneself and hanging a friend in play are dangerous experiments, because they are likely to become too realistic. Ziemke[7] points out that unconsciousness in hanging is not due to lack of blood in the brain, but to lack of arterial blood, or of oxygen. Anemia of the brain, when found after death from hanging, exists before suspension. The compression of the arteries arrests the flow into the brain and when incomplete it may lead to venous engorgement.

While unconsciousness follows suspension instantaneously, death does not follow until after the lapse of some minutes. While there may be immediate arrest of the heart through the vagus center, this is only transitory and the heart beats begin again. The time that elapses between suspension and permanent arrest of the heart is variable. Usually the heart permanently ceases to beat within from five to sixteen minutes. In attempts at suicide the occlusion of the blood vessels is often incomplete and for this reason recovery may follow relatively long periods of suspension. The symptoms observed in those who have recovered from hanging are variable. There may be paralytic symptoms, especially of the bladder and bowel. Difficult respiration, bronchial catarrh, expectoration of blood and more or less protracted fever have been observed. The symptoms referable to the central nervous system, such as convulsions, sensation anomalies and hallucinatory delirium, have given rise to considerable discussion and the expression of marked differences of opinion. In some there are marked contortions, in others there are seizures resembling those of epilepsy, while in many there is extraordinary increase in reflex excitability. Some authorities hold that most, possibly all, of these manifestations are hysterical. It is worthy of note that in persons who have recovered from hanging there may be a retroactive amnesia, in which the victim may fail to remember not only everything connected with the hanging but events that happened before that time.

While in legal execution by hanging the body is dropped some distance, in suicide the body may have any position that man may voluntarily assume. In 261 cases, Tardieu found 168 with the feet touching the ground, 42 on their knees, 25 lying horizontally and 19 sitting. Brouardel has determined the weight necessary to cut off the flow of blood through the vessels of the neck and has found that two kilos compress the jugular veins, five close the carotids, fifteen shut the windpipe and thirty occlude the vertebral arteries. Besides the weight suspended, the nature of the cord is an important factor, a narrow cord being more effective than a broad one. Moreover, the presence of something,

such as a long beard, articles of clothing, or tumors of the neck, under the cord, have an effect.

It seems that some writers have overdrawn the unsightly appearance of the face of the hanged. As a rule the face of one who has come to his death by suspension does not differ from that of those who have died from other forms of violence. Occasionally there is marked cyanosis of the face but Schmidt found this condition in only 24 out of 344 deaths from hanging and Reuter did not observe marked cyanosis once in 200 cases. Ziemke[8] states that the description of the face of the hanged as given by Martin is a "phantasy picture." He also says that he has not seen unequal dilation of the pupil and the open lids more frequently in the hanged than in those dying from disease. Ecchymoses, from the size of a pin point to that of a pea, are sometimes, not always, found on the forehead, on the lids and in the conjunctivæ, less frequently in the skin of the neck and chest. Lochte saw these in only eight out of 80 deaths by hanging. Schmidt observed conjunctival ecchymoses in 133 out of 344 cases, and Martineck in 17 out of 184. While these ecchymoses are found sometimes in the hanged, they also are seen in deaths from other forms of violence. Ziemke found ecchymoses in the conjunctivæ and gums of a child that had been killed by a blow with a hammer on the forehead and then hung. Rupture of the ear drum, it seems, may result from hanging but is by no means frequent.

The location of postmortem ecchymoses on the body may be of service in the examination of the hanged, but ordinarily they do not differ in distribution from those observed in the dead from other causes. The fluid state of the blood leads to the ready appearance of areas of hypostatic congestion and since the hanged are usually soon cut down and given a horizontal position they are most frequently seen on the back. However, when the body remains suspended the hypostatic areas of redness are seen mostly, or exclusively, in the dependent parts, especially in the limbs. The exclusive location of these congested spots in the dependent portions of the body, especially if they remain in these locations after the body has been placed in the supine position, is stated by Ziemke to be proof that the body has been suspended at least eight hours, because after this time the ecchymosed blood does not change its position with changes in the posture of the body. The fluid blood soon after death gravitates to the lowest parts of the body and when the hanged man is on his knees the thighs may show large areas of ecchymoses, while these stains may be wholly lacking below the knees. In one instance Schmidt found that the downward flow of the blood was arrested by tight garters.

Much has been written about the occurrence of a sexual orgasm in death from hanging, because the penis has occasionally been found to be erect and the underclothing stained with seminal fluid. That the ejaculation of semen does occur in some instances cannot be denied, but that there is any pleasurable sensation connected with this act, there is not the slightest reason for believing. Death from asphyxia whether caused by mechanical means or by the administration of a poison that acts on the respiratory centers, is often accompanied by the ejaculation of semen. Turgescence of the sexual organs in both sexes after hanging is common.

The appearance and character of the groove or mark made by the cord about the neck are worthy of the closest study. It seems that everything long

enough and sufficiently pliable has been tried by the suicide who has chosen hanging as his mode of exit. Rope, cord of every kind, leather straps, wire, suspenders, garters, cravats, handkerchiefs, towels, sheets, twisted straw, bark and pliable limbs of trees are some of the things which the ingenuity of the suicide has converted into a hangman's noose. It is quite evident that with such a variety of cords the marks and grooves must differ greatly in appearance. Then, there are differences in the adjustment of the noose that affect the shape, size and course of the line of strangulation. The more cautious suicide prepares a slip noose with the cord going all around his neck and so arranged that it tightens down when he throws his weight on it. The less skillful man prepares an immovable loop, which he places under his chin and then throws himself forward, steps from a chair, or bends his knees, or in a sitting, squatting or even in a horizontal position presses against the cord until the circulation to the brain is arrested, which, as has been seen, may be instantaneous, when he loses consciousness and is no longer able to extricate himself or to call for help.

When a broad piece of cloth as a folded towel or sheet, or a broad band of any material, is employed there may be merely a slight discoloration along the path of application and in rare instances this may be so superficial, especially when the body is removed from the noose soon after death, that it wholly disappears before the legal inspection is made. Strassmann reports such an instance: A man hung himself with a silk scarf, the body was taken down after fifteen minutes, and at the obduction no trace of the mark could be detected. Maschka reports a similar instance in which every visible sign of the local effect of the noose disappeared within twenty-four hours. It is said that when the strangulation mark is slight and the body is placed in water the discoloration may shortly disappear. This is one extreme while at the other a wire cord may cut into the soft tissues and when the body is left suspended for some hours it may sink into the vertebræ. Even when a broad band has been employed it may be that a seam in it or one edge may act like a thin cord and make a deep groove, or there may be a broad mark and a deep narrow groove. It is customary to speak of two kinds of strangulation marks. One is pale in color and soft in consistency. It is due to the gradual pressure of a broad, soft band, which slowly removes the blood from the part directly pressed upon while just outside of this area, both above and below are lines of congestion, which may become more deeply colored from hypostasis. In these instances the line of compression is generally gray or grayish-blue, although when superficially observed it may appear quite pale. The second kind of strangulation line is brown in color, dry and hard. This was once called a mumification line and was believed to occur only when the epidermis was destroyed by the constricting cord, but the microscopical studies of Schulz have shown that it is not so much due to abrasion of the epidermis, as to the removal of the fluids of the tissue by greater compression. This author distinguishes between a leather-like and a parchment-like line, the latter differing from the former in the greater intensity of the pressure and the consequent greater drying out of the tissue. Both become darker, drier and harder on exposure to the air, due to the evaporation of fluid. The dry, hard, dark lines most frequently result from strong, narrow cords, such as small ropes and especially from binding twine.

It was once supposed that sugillation in the strangulation line always oc-

curs when death results from hanging and that it never occurs in a suspended corpse, but more thorough investigation has shown that it is the exception, though it may occur in death from hanging, and that it may also be found in a suspended corpse; therefore, sugillation alone is no proof that the hanging was done during life.

It was suggested by Neyding[9] that the microscopical demonstration of pinpoint hemorrhages in the compressed tissue might be taken as an evidence that death was caused by hanging, but others have shown that these may occur in a suspended corpse. Greater stress should be placed upon the macroscopic vascular congestion along the edges of the strangulation line, but this must not be confounded with postmortem hypostasis.

When the cord is brought two or more times about the neck there will be multiple strangulation lines with intermediate crests and sugillation in the latter may be marked. It is easily evident that the blood is forced into these crests by the constrictions above and below and this has been taken as evidence that death was due to hanging and taken with other things it undoubtedly has its value, but alone it is not convincing proof because the coloration may be due to postmortem diffusion, and when observed in a hypostatic area the livid crest is without value in determining the manner of death. However, Bockavius[10] thinks that the character and localization of the vascular hyperemia and the nature of the extravasations both along the strangulation line and in the crests, when these exist, may be of diagnostic value when studied microscopically. He thinks that when these hyperemias and extravasations occur during life they are due to an active vascular congestion and that this may be recognized microscopically by the fullness of the arterioles, which in death are empty, and in death the only congestion possible is venous. This is a fine distinction and in the hands of an expert it may be of great service, but without unusual experience it might be difficult to distinguish between the smallest veins and arteries, especially when they are filled with blood.

Rarely blisters filled with serum more or less colored with blood are found along the strangulation line and in the crests, when these exist. It would seem that these could hardly occur in a suspended corpse, but Schulz says that they may. At any rate they are so infrequently observed in death from hanging that but little diagnostic value can be attached to them.

In the study of strangulation marks and grooves due to hanging some most unexpected questions have arisen. It has already been seen that these marks may be so slight that they are not easily recognized and that they may soon wholly disappear. On the other hand, it has been found that in rare instances lines and grooves resembling those caused by the noose have been found to be due to other causes. Ziemke states that the creases in the necks of fat (and dirty) children may show marks closely resembling those due to a noose, and Maschka relates the case of a little girl who had a narrow band of some inflammable material about her neck. This caught fire and quickly burning there was left about the neck a line similar to that of a noose. Lesser tells of an epileptic that was found in the morning with his face on the floor and his legs on the bed and that the collar of his nightshirt had produced a strangulation line about his neck, but Ziemke suggests that possibly this man actually died from hanging.

Examination of the viscera after death by hanging shows nothing that is

strictly characteristic. When all the vessels of the neck are completely occluded by the cord, blood can neither enter nor leave the brain. Profuse hemorrhage in the cranial cavity after death by hanging is rare and probably occurs only when the vessels are diseased and consequently are easily ruptured. However, it is not strange that sudden arrest of the circulation in the brain may lead to moderate engorgement, which is likely to be greater when the arterial flow is only partially obstructed. Instances of paralysis among those who have attempted suicide by hanging and have been found in time to save life have been reported. When the brain is found to be anemic, as is sometimes the case, it must have been in this condition before the tightening of the cord, because, as has been seen, the jugular veins are easily compressed. Retinal and retrobulbar hemorrhages seem to be very rare, but have been observed.

Severe pulmonary hemorrhages are rare, but have been seen, especially in the tubercular. The quantity of blood in the lungs after death from hanging is very variable. It is probably largely determined by the coincidence of the drop with expiration or with inspiration. In the former instance the pulmonary vessels contain less blood than they do in the latter. Lochte[11] thinks that the degree of compression on the vessels of the neck has much to do with the volume of blood in the lungs. In incomplete closure of the vessels the duration of asphyxia is lengthened and passive hyperemia of the lungs and other organs may take place.

Edema of the lungs, generally confined to one lobe and sometimes to a part of a lobe and resulting from a terminal stasis, has been observed. Lochte found it in 23 out of 71 cases of suicide by hanging and Strassmann has seen it especially when the knot lies over the throat. He thinks that cyanosis of the face and edema of the lungs occur only when the occlusion of the vessels is incomplete but that they do not always occur when this condition prevails.

Sometimes hemorrhages are found in the mucous membrane of the alimentary canal. Ziemke is of the opinion that in the majority of instances they result from hypostasis, but that in some there is rupture of the smaller blood vessels during the convulsions of asphyxia. The writer wishes to suggest that punctiform hemorrhages in the mucous membrane of the stomach occur frequently in the convulsions of asphyxia whether the failure of respiration is due to mechanical pressure on the larynx or to the administration of a poison that acts upon the respiratory center. Hemorrhage into the stomach, which could not be due to hypostasis, has been reported by such careful observers as Tourdes, Lesser and Hofmann after death by hanging. Tourdes observed gastric hemorrhage in 31 out of 60 cases of death from hanging.

Occasionally food from the stomach has been found in the larynx and more rarely in the fine bronchi. In the former instance it is likely that the handling of the body in taking it down may account for the bits of food found in the larynx but they could be carried to the smaller bronchi only by inspiration and must be transported before the windpipe is occluded.

Ziemke gives the following directions for the dissection and examination of the neck after death from hanging: After the separation of the skin from the fascia and muscles, the musculi omo-hyoidei should be divided in the middle on the inner border of the musculi sterno-cleido-hyoidei and dissected out, then the sterno-cleido-mastoidei should be separated from attachment to the

clavicle and the sterno-hyoidei from the hyoid bone, and the deeper lying sterno-thyroidei and thyreo-hyoidei should be severed, dissected out and turned back.

Hemorrhage of the deeper soft tissues of the neck after death by hanging is not frequent. Martineck observed this only ten times out of 184 cases and Schmidt eleven times in 344. It is more frequent after legal execution than in suicide owing to the greater violence with which the former is done. Marked hemorrhage in or between the muscles of the neck is regarded as conclusive proof that the injury was inflicted during life. Laceration of the muscles of the neck is also rare in suicide. The most important findings in dissection of the neck consist of fractures of the cartilages of the larynx, of the thyroid and of the hyoid bone. Fracture of one or more of these structures occurs probably in the majority of cases of death from hanging. Fracture or displacement of cervical vertebræ may occur when the drop is great as it is in legal execution, but is infrequent in suicide. Rupture of the intima of one or both carotids may happen and there is one case reported from the Berlin forensic institute in which there was rupture of the intima of the jugular vein.

The question whether death was self-inflicted or not is an important one and deserves further study. Leaving out of consideration all instances of legal execution and of mob violence in which as a rule there is no room for doubt, the decision between suicide and murder will be discussed. In the first place it should be stated that hanging is a common form of suicide and a rare one for murder, so that the presumption is in favor of the former, but this does not relieve the one who investigates the case from the necessity of exercising the greatest care. The fact that hanging offers a speedy, painless and noiseless death and that the means of carrying it out are always at hand probably explains its frequent selection by the suicide. On the other hand it is not easy for one person to hang another if the victim is aware of the intention of his assailant, unless the latter is much superior in strength to the former. Children and old and feeble people may be hung, but this is not, as has been stated, a frequent resort of the murderer.

When a body is found freely suspended with nothing at hand whereby such a position could have been reached, help in the execution of the deed must be evident.

The suicide often leaves some record of his intention and his clothing and his belongings should be carefully searched for such evidence. If a written statement be found the question becomes one of identification of the handwriting. Bodily infirmities in the form of incurable disease, involving continuous suffering, financial losses, family disagreement and melancholia from any cause are some of the conditions that lead to suicide.

The cord used in the suspension should be examined. Where did it come from, to whom did it belong or in whose possession was it, are questions that arise naturally. As a rule the suicide selects something that will not cut deep with the idea that it will cause less pain. For like reason the suicide, as a rule to which, however, there are exceptions, does not provide for a long drop.

The fact that the victim is a child will be taken into consideration but children as young as eight or ten years have been known to commit suicide in this way. The presence of wounds on the body must be investigated. These do not, however, preclude suicide and many cases are recorded in which at-

tempts to destroy one's own life have been repeatedly made and not proving successful hanging has been resorted to. In some instances attempts have been made to cut the throat or to open an artery, but courage or skill being lacking, the noose has been employed; in others, poison has been taken.

There are a few cases, the number is not large, in which people have been killed in some other manner and then the dead body has been suspended by the murderer in order to present the appearance of suicide. Vrolik tells of a sailor who was stabbed through the heart. His murderer washed the body, dressed it in a clean shirt and suspended it. Maschka reports the finding of a suspended corpse the skull of which had been fractured by a blow. Gross tells of a man who drove a long, sharp needle through the chest wall, under the breast of his wife, into her heart and then suspended her body. If one has been strangled to death and then suspended it might be quite difficult to determine the cause of death unless the imprint of fingers on the throat be found. Lesser reports an instance of a man who, while sitting on a stool, was approached from behind, a cord was thrown about his neck and twisted. He fell from the stool in an unconscious state and after his death his body was suspended by his assailant.

Ziemke[12] gives the following as proofs that hanging was the cause of death:

1. Profuse effusion of blood under the strangulation groove when shown not to be due to hypostasis.

2. Marked vascular congestion along the edges, especially the lower edge of the strangulation groove, which is found on macroscopic examination to consist of a network of distended vessels, when this is shown with certainty not to be due to hypostasis.

3. A large number of isolated blood vessels that pass through the groove of strangulation are filled with blackish-red blood and are brought out more distinctly by treatment with alcohol-xylol.

4. A red intermediate crest, if it is broad and remains prominent and firm after the removal of the cord, lies in paler skin and is found on microscopic examination to consist of congested vessels and hemorrhages into the cutis and subcutaneous fat.

5. Profuse hemorrhages in and between the muscles of the throat and lacerations of the muscles and fractures of the larynx with profuse blood extravasations, when shown not to be due to hypostasis.

6. Lacerations of the intima of the carotids with extravasated edges and hemorrhages into the sheath of the vessel.

7. Marked cyanosis of the face, with numerous small hemorrhages in the skin, which extend down to the groove and stand out in contrast with the paler surface of the rest of the body.

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—*V. C. V.*